



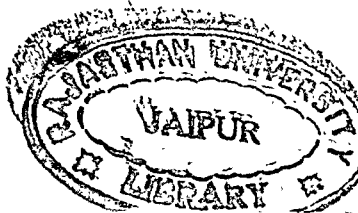
# ANNALS *of* ALLERGY

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# ANNALS of ALLERGY

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# ANNALS *of* ALLERGY

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Volume 3

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Number 1

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## THE GROWTH AND DEVELOPMENT OF ALLERGY

### A Ten-Year Study of One Hundred Allergic Children from Birth to Ten Years of Age

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Seattle, Washington

WHAT happens to infants who exhibit allergic manifestations during the first few months of life? Do they develop other types of allergy as they grow older? Do they "outgrow" their allergic symptoms? When do these symptoms develop and what is the course of the allergic cycle in the growing child? Ten years ago in an article by the same author entitled "Allergy in Infants, the Significance of the First Allergic Manifestations," several statements were made. First was the fact that 80 per cent of allergic infants developed their first allergic symptoms or "shock" before they were four months old. Second, the conclusion of that article raised a question, namely—"As a result of these observations, I believe that the significance of diagnosing the first allergic manifestation in infancy is primarily that of recognizing the presence of an allergic state. Specific attention to the diet and environmental factors during childhood may prove to be important prophylactic measures in preventing or minimizing the major allergic diseases." This paper will attempt to answer this question.

The present study is a follow-up of 100 allergic infants over a period of from ten to fifteen years. All patients were seen in private practice from birth to the present. They were examined and treated regularly for routine preventive care as well as for acute illnesses. During this time it was my pleasure to know the child and his parents, and their reaction to his physical and mental problems. All examinations, diagnoses, treatments, records and conclusions were made by the author, so that this factor is common to all the patients over the entire period of this analysis. I was particularly interested in finding out what happens to these allergic

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people. If we feel that an infant is a potential candidate for hay fever, hives, or asthma, is it within the realm of our knowledge to do anything about it? Are specific prophylactic allergic measures begun early in life of any value in preventing major allergic disease? No attempt will be made to discuss methods of diagnosis or treatment, other than a few general conclusions presented by this study.

Two types of allergic symptoms will be discussed: (1) the early infant group consisting mainly of a rash, vomiting, and gastro-intestinal symptoms; (2) the major allergic diseases, namely perennial allergic rhinitis, pollen hay fever, asthma, eczema, hives, and gastro-intestinal symptoms.

It is significant to every pediatrician as well as those physicians who treat infants and children to know that approximately 82 per cent of the allergic babies develop their first allergic symptom by four months of age; 39 per cent have their first allergic shock by one month of age, and 24 per cent by two months. A few in this study (11 per cent) did not develop any allergic manifestation until they were between the ages of one and ten years. For practical purposes we may label most of these infants as "allergic" before they are four months old.

The early allergic manifestations are of three rather distinct types, several of which may occur in the same patient at the same time. These symptoms were considered allergic because they disappeared with the elimination of the offending allergen and reappeared when the causative food or other factor was added. The clinical trial verified the diagnosis.

The rash or eczema was present in fifty-three cases and was usually due to some food, especially orange juice. Vomiting, or pylorospasm, occurred in thirty-six cases. This symptom was usually due to orange or milk, and was relieved by the substitution of other foods. Gastro-intestinal allergy consisting of severe persistent colic, excessive gas, recurrent diarrhea or constipation, was present in twenty-three infants. Ten years ago when raw egg yolk was routinely added to the milk formula of all infants at one or two months of age, 90 per cent of the allergic babies receiving raw egg yolk developed a rash, pylorospasm, or gastro-intestinal distress as their first allergic symptom. In a similar nonallergic group of babies, there were no allergic symptoms from egg yolk. In the present series egg yolk was not added to the diet of allergic babies until one year of age. Orange juice was the single most important allergen producing the initial allergic sensitization or shock. Cod liver oil was an occasional factor but it is becoming less important as we use more of the natural concentrates and the synthetic vitamin D preparations.

In three cases each, the original allergic insult was one of the more serious types of allergy, such as asthma, perennial rhinitis, and pollen hay fever. The "allergic tongue" was the symptom first noted in three cases. This type of tongue lesion consists of "hive"-like bald areas, circinate, with slightly raised reddish borders usually on the edges or tip of the tongue. These symptoms are due to food allergy and are aggra-

# GROWTH AND DEVELOPMENT OF ALLERGY—CLEIN

TABLE I. AGE OF DEVELOPMENT OF FIRST ALLERGIC SYMPTOM IN 100 INFANTS

Age	1 mo.	2 mo.	3 mo.	4 mo.	5 mo.	6-12 mo.	1-2 yr.	2-6 yr.	6-10 yr.
No. of Cases	39	24	13	6	2	5	3	5	3

82 per cent developed first allergic symptom by 4 months of age.

89 per cent developed first allergic symptom by 1 year of age.

TABLE II. FIRST ALLERGIC SYMPTOM MANIFESTED BY CASES

RASH (Eczema)	53
VOMITING (Pylorospasm)	36
GASTRO-INTESTINAL DISTRESS (More or less persistent colic, gas, diarrhea, constipation)	23
ASTHMA	3
ALLERGIC RHINITIS (Perennial)	3
ALLERGIC TONGUE (Geographic)	3
HAY FEVER (Pollen)	3
HIVES	1
Several symptoms may occur in same patient at same time.	

TABLE III. TYPE OF MAJOR ALLERGIC DISEASE DEVELOPING IN 100 PATIENTS OVER TEN-YEAR PERIOD

No Major Allergy Developed	20	Analysis of Gastro-Intestinal Symptoms	Cases
ALLERGIC RHINITIS (Perennial)	59	ABDOMINAL PAIN (Severe-chronic-recurrent)	7
HAY FEVER (Pollinosis)	38	DIARRHEA	3
ASTHMA	26	ACIDOSIS (Cyclic Vomiting)	2
ECZEMA	33	CLAY-COLORED STOOLS (Hepatitis)	2
GASTRO-INTESTINAL	20	CANKER SORES	2
HIVES	10	PRURITUS ANI	2
SWELLING OF EYES	2	MUCOUS COLITIS	1
MIGRAINE	2	DUODENAL ULCER	1
ITCHING SKIN (Persistent)	2		
CAROTINEMIA	8		
ALLERGIC TONGUE	7		
MERCURY SENSITIVITY (Ointment)	1		
Several symptoms may occur in same patient			

TABLE IV. RELATIONSHIP OF MAJOR ALLERGIC SYMPTOMS AND THEIR COMPLICATIONS TO EACH OTHER

Cases	Perennial Rhinitis		Hay Fever Pollens		Asthma		Eczema	
	No. Cases	%	No. Cases	%	No. Cases	%	No. Cases	%
Perennial Rhinitis	59	26	21	32	12	20	21	32
Hay Fever (Pollens)	38	21	55	17	9	24	12	32
Asthma	26	12	46	8	30	6	8	30
Eczema	33	21	65	12	32	8	24	7

TABLE V. CHILDREN HAVING ONLY ONE MAJOR ALLERGIC DISEASE, UNCOMPLICATED

PERENNIAL RHINITIS	26
HAY FEVER (Pollen)	17
ASTHMA	6
ECZEMA	7
Total	56

vated by tart or "acid" foods. In later years, these lesions assume the appearance of what is commonly known as the "geographic tongue."

It is amazing to note that only two of the 100 infants *did not develop any major allergic disease* to their present ages of ten and twelve years, respectively. It is equally shocking to realize the exceedingly high incidence of those developing the so-called major allergic symptoms. *Ninety-eight of 100 allergic infants developed major allergic symptoms* in their first ten years.

#### PERENNIAL ALLERGIC RHINITIS (THE ALLERGIC NOSE)

Perennial allergic rhinitis was the most prevalent type of major allergy, and included those patients that are bothered by a "stuffy nose." These patients are usually worse during the night, because most of their symptoms are due to inhalant allergens. A short time after the patient awakens in the morning these symptoms may disappear. They recur during the daytime if food allergy is also a factor. These symptoms are more common in the winter since the patient spends more time indoors. They may have an associated pollen allergy in the summer.

The child with frequently recurring colds, "who no sooner gets over one cold before he catches another," is usually of this type. A chronic runny nose, sniffles, and occasionally a night cough are present. A temperature rise is usually not present except with an associated infection. Fifty-nine patients (59 per cent of the entire group) had this symptom. Several or all types of allergy may occur in the same patient. In other words, of fifty-nine perennial rhinitis cases, one-half had rhinitis as the only symptom, one of every three of these patients also had hay fever or eczema, and one of every five had asthma.

#### HAY FEVER (POLLINOSIS)

Seasonal hay fever or pollinosis was present in thirty-eight of the 100 cases. It was second in frequency of occurrence. These patients were mainly grass-pollen sensitive and a few tree-pollen cases. Fall hay fever is not a problem as we do not have ragweed in the Pacific Northwest. Grass hay fever was the only allergic symptom present in seventeen children. One-half of the pollen hay fever group also had perennial rhinitis, one-third had an associated eczema, and one-fourth of the grass-pollen patients had asthma.

#### ASTHMA

Asthma occurred in twenty-six patients ranging from the age of one month to twelve years. It was the *only* major allergic symptom in 6 per cent of the entire series. The diagnosis was apparent by the typical physical findings, wheezing, and labored breathing. This symptom was complicated with perennial rhinitis in about one-half of the total asthmatics; with hay fever in one-third of the cases and with eczema in about one-third of the asthmatic children. There were very few cases of severe asthma,

and it was extremely rare for any of these patients to require hospital treatment. The pre-asthmatic cough (Table VII) was present in some cases but did not always develop into asthmatic wheezing.

#### ECZEMA

The varied types of rashes classified as allergic eczema were found in thirty-three patients. Many of the rashes which occurred as the first allergic manifestation disappeared within a relatively short time due to omission of the causative food, contact, or inhalant. Those that remained or recurred and became chronic problems are included in this group. Two-thirds of this eczema group also had allergic rhinitis, one-third had pollen hay fever, and one-fourth had asthma as a complication or as an associated allergic symptom. Eczema was the only major allergic symptom in 7 per cent of the entire series of 100 children.

#### GASTRO-INTESTINAL

Symptoms referable to the gastro-intestinal tract were varied, but very definite. The most common complaint was abdominal pain. This was often severe, recurred frequently, and followed no definite pattern as to time, location, or duration of the pain. Physical and laboratory findings were usually normal. Recurrent diarrhea, often alternating with constipation, was present in three cases. Cyclic vomiting causing severe dehydration, recurring with an acute infection, was a serious problem in two children. Once the allergic factor was under control, these symptoms disappeared. Clay-colored stools with no jaundice, but with abdominal pain, was present in two patients due to definite food allergy. Canker sores are a fairly common occurrence, but not often as severe as in two of these children. Pruritus ani, causing great distress, due to citrus fruits, occurred in several children. One case each of mucous colitis and duodenal ulcer were relieved by allergic management. The gastro-intestinal symptoms would disappear when the offending food allergens were avoided, and recur when these were added to the diet.

#### HIVES

Ten cases of hives, including two of severe angioneurotic edema were encountered in this group.

Other symptoms observed were: swelling of the eyes in two patients; migraine, 2; persistent itching skin, 2; carotinemia, eight; allergic tongue, seven; and mercury sensitivity and petit mal epilepsy in one case each.

Apparently, the first allergic symptom, such as a rash or pylorospasm, does not influence or predetermine the type of major allergy that will develop in later years. For instance, an infant having an allergic rash as the first symptom does not necessarily develop eczema later; he may develop any type of allergy at any time. The chart shows that infants having an



# GROWTH AND DEVELOPMENT OF ALLERGY—CLEIN

TABLE VI. DOES THE FIRST ALLERGIC SYMPTOM INFLUENCE OR DETERMINE THE TYPE OF MAJOR ALLERGY WHICH DEVELOPS LATER?

First allergic symptom	No of Cases	Subsequent major allergic disease					
		Eczema	Allergic Rhinitis	Hay Fever	Asthma	Gastro-Intestinal	Hives
Rash (Eczema)	53	22	31	18	15	6	4
Vomiting (Pylorospasm)	36	14	24	14	8	11	6
Gastro-Intestinal (gas, colic, diarrhea, constipation)	22	2	5	5	8	4	2

Approximately the same number of children developed perennial allergic rhinitis, hay fever or asthma, whether the first symptom was a rash or vomiting. A larger number of the original "vomitters" developed gastro-intestinal allergy or hives than the "rash" or "G.I." groups. Those with early gastro-intestinal symptoms developed fewer cases of hay fever or eczema than the other groups.

TABLE VII. AGES AT WHICH MAJOR ALLERGIC SYMPTOMS DEVELOP IN INFANTS HAVING EARLY ALLERGIC MANIFESTATIONS

Major Allergic symptoms	No. of Cases	Age in years									
		1	2	3	4	5	6	7	8	9	10
Allergic Rhinitis (Perennial-frequent colds)	59	13	10	8	10	3	4	5	4	1	1
Hay Fever (Pollen)	38	2	4	10	7	4	3	2	4	1	1
Asthma	26	7	4	2	2	4	4	2	1		
Eczema	33	23	4	3	1		2				
Hives	10	1	4	2			2	1			
Gastro-Intestinal (Abdominal pain-cankers-diarrhea-constipation-colitis-pruritis)	20		3	4	1	3	4		3	1	1
Migraine	2						1		1		
Allergic Cough (pre-asthmatic)	30	6	7	5	3	5	1	1	1	1	
Total		52	36	34	24	19	21	11	14	4	3

76 per cent of major allergy developed the first five years.

85 per cent of major allergy developed in the first six years.

Conclusion: Only a small percentage (15 per cent) developed major allergy after six years of age. Early diagnosis, prophylaxis, and treatment are of great importance in preventing the development of major allergy after six years of age.

TABLE VIII. CHRONOLOGICAL ORDER IN WHICH MAJOR ALLERGIC DISEASES DEVELOP IN THE GROWING CHILD

Major Allergic Symptoms	No. of Cases	Order of Appearance			
		1st	2nd	3rd	4th
Allergic Rhinitis (Perennial-frequent colds)	59	31	24	4	
Hay Fever (Pollen)	38	12	15	10	1
Asthma	26	10	6	7	3
Eczema	33	28	4		1
Hives	10		6	3	1
Gastro-Intestinal	20	10	4	4	2
Migraine	2		1	1	

Several diseases may occur in the same patient

ECZEMA, when present, was usually the first major allergic symptom because it persisted from the onset of the first allergic "shock" in infancy (twenty-eight out of thirty-three cases). ALLERGIC RHINITIS (frequent colds) developed earlier and more frequently as the first major allergic symptom (53 per cent). This most common allergic symptom followed eczema, asthma, and other GI allergic diseases as the second type of allergic manifestation (40 per cent) in this cycle.

initial rash or vomiting later developed allergic rhinitis, hay fever, or asthma in about the same proportion. Those that had pylorospasm in infancy developed more gastro-intestinal allergy and hives than the other two groups. Those with early gastro-intestinal symptoms had less chance of developing eczema as they grew older.

The age at which these infants and children developed their major allergic diseases is interesting because they occurred much earlier than commonly recognized. These figures are based on the age when the particular symptom was first diagnosed. There were more eczema cases in the first year as these were mainly infants in which the rash persisted and became chronic. Of the major allergic symptoms 76 per cent were diagnosed in the first five years and 85 per cent in the first six years. This means that most of our major allergic symptoms in children are pre-school-age problems. It is possible and probable that the early diagnosis and treatment were of great importance in preventing these diseases from becoming more severe, more complicated and more difficult therapeutic problems during the school age. The results of the prophylactic and active treatment of these "virgin" allergic cases appears to be more effective, rapid, and thorough, and there is less tendency for recurrence than in other groups of allergic children treated for the first time only after their major allergic disease had been well developed.

Pollen hay fever occurred more frequently in the three- and four-year-old group. These symptoms occur clinically in a mild form in many children, although the skin tests are frequently negative during the first few years. The nasal secretions often reveal an increased eosinophilia which is diagnostic. This is also true in most patients with the perennial type of allergic rhinitis.

There is not much regularity in the chronological order in which the major allergic diseases develop in the allergic cycle that occurs from infancy to adolescence. Perennial rhinitis was more often the first major symptom following the initial allergic shock in infancy. Thirty-one cases developed first in this group; twenty-four cases developed second, that is, after asthma, eczema or hay fever was already present; four cases occurred only after two other allergic symptoms had developed.

Pollen hay fever usually followed the perennial type of allergic rhinitis in this cycle of development. Two-thirds of the cases of hay fever developed as the second or third symptom in this chronologic lineup. In twelve patients, pollen hay fever was the first symptom of major allergy. Asthma was the first major allergic disease in ten cases. This is significant inasmuch as asthma is often considered the final development in the allergic cycle, instead of the first. The remaining types of allergy were about equally divided as to whether they happened to be the first, second, or third phase in the pathogenesis of major allergic disease.

# GROWTH AND DEVELOPMENT OF ALLERGY—CLEIN

## RESULTS OF TREATMENT

A short discussion of the results of treatment will be mentioned. Treatment was of the pediatric allergic type. These patients were considered primarily as a pediatric problem requiring the use of allergic methods of diagnosis and treatment. More chronic allergic disease in children has been unrecognized than any other type of illness. In many cases, if the diagnosis is made, treatment is inadequate. The most grateful parents are those whose allergic children have been successfully treated and relieved by allergic methods. These children had been treated with vitamins, cold shots, light treatments, tonics, change of climate, autogenous vaccines, and tonsil and adenoid operations, without any previous relief.

Treatment consisted of elimination, substitution, and avoidance of irritating factors such as foods, inhalants and contact substances. Since the infant is exposed to fewer foods and perhaps fewer external or inhalant factors than the adult, the diagnosis and treatment of his "virgin" allergic problems is often simplified. Fifty-three children required testing when other methods were unsuccessful. Twenty-eight were given desensitization treatments with specially prepared individual antigens, consisting of inhalants such as pollens, epidermals, dust, and molds.

The present health of these children, in a general way, is about the same as that for any other equivalent group of children physically and mentally. The results of treatment were as follows:

Excellent results (no symptoms).....	73
Good results .....	16
Fair or not much improved.....	11

Fifty-three remained clinically normal if they observed their diet schedule. Forty-two were well if they avoided the environmental factors that bothered them and in some cases continued to receive their specific antigen. Fifteen were normal on an unrestricted diet and without observing any special environmental rules.

The co-operation of the parent naturally has a great deal to do with our final results. It is much more difficult to control the diet, rest and environment of a child than that of an adult. After many years of contact with these parents and the children, their co-operation was appraised as "good" in fifty-five cases, "fair" in thirty-five and "poor" in ten. In other words, in almost 50 per cent of the cases we had little help from the parent. This means that many important prophylactic measures were never carried out and that our chances of success were only about 50 per cent of what they should be even with the best treatment. Of these cases, 76 per cent were treated early when the diagnosis was first made; that is, they were tested, treated, given antigen when necessary, and the application of other

standard measures. The remaining 24 per cent were treated only after the major allergic symptoms recurred or became annoying or more serious. We cannot expect as good results from treatment of a "full-grown" disease as we can from an early case.

The present health status of allergic children depends not only on our accepted methods of diagnosis and treatment, but equally on the co-operation of the parent, the time of starting and continuing treatment, and the opportunity for occasional consultations with the well child and his parents. The attitude and co-operation of the child depend a great deal on that of his parents.

The tonsil and adenoid question is always important. Sixty-one children had their tonsils and adenoids removed. The indications were the same as those for children who are not allergic. The general health of the allergic child was improved in this manner. The allergic problem was always treated first, then surgery was performed if the symptoms still warranted this method of treatment.

#### COMMENT

The foregoing discussion has shown that practically *all allergic* infants develop major allergic disease or symptoms as they grow older. The standard accepted prophylactic measures failed to prevent these symptoms. Rigid dietary restrictions and specific environmental control factors begun in infancy, even when carried out faithfully and with excellent co-operation, did not prevent the development of hay fever, asthma, and other major allergies. There is no question that the symptoms were usually milder, reacted more readily to treatment and that there were fewer and milder recurrences. This adds up to the fact that proper treatment means fewer sick days, fewer days out of school, more active exercise and engagement in life's daily routine for these children. Since children play in "high gear" most of the time, this is quite important.

Ten years ago, when egg yolk was eliminated from our infant feeding formulae, the number of early allergic symptoms dropped appreciably; eighty-five of the 100 allergic infants in the original series ten years ago had a rash or eczema. When egg yolk was discontinued, the next group of 100 allergic infants had a rash in only fifty-three cases. This is a reduction of about one-third, meaning that fewer babies were given their first allergic sensitization. Since orange juice is also such a constant sensitizing food, we have eliminated this in any baby who has a family history of allergy or whose brothers or sisters have allergic problems. This has considerably reduced the initial allergic factors by about another one-third. Synthetic Vitamin C or other natural foods rich in Vitamin C such as banana, furnish adequate requirements of this vitamin. Of equal importance is a dust-free nursery for the infant, as inhalant factors are much more important than commonly considered.

If we cannot prevent allergy, have we been able to conquer its symptoms? Of these children, 76 per cent developed their major allergic prob-

lems before school age. Only 15 per cent developed major allergy after six years of age. It was formerly believed that most asthma and hay fever developed in the pre-adolescent age. This was probably due to the fact that frequently medical care was not sought until the condition became serious enough to consult a physician. This suggests that the early diagnosis, prophylactic, and active treatment relieved the first symptoms sufficiently so that there were fewer remissions. Those that did recur were usually much easier to control.

Another important observation was that the treated allergic children "went through" measles, pertussis, and other severe infections without any more trouble than nonallergic children. Many textbooks claim 20 to 40 per cent of asthma in children develops after the acute infections. This is probably true in allergic children that have not had the benefit of prophylactic and active treatment. In this type of case, latent or potential allergy flares up as the result of the severe stress and strain of the infection.

#### SUMMARY

1. One hundred children having allergic manifestations in infancy were observed for at least ten years. Their first allergic symptoms usually occurred in the first four months of life, and were present as a rash or eczema, vomiting or pylorospasm, and gastro-intestinal distress such as colic, excess gas, diarrhea and constipation. Egg yolk and orange juice were the most common allergens in infancy.

2. When these infants were labeled "allergic," prophylactic dietary and environmental treatment was instituted and was stressed repeatedly at each examination.

3. Ninety-eight per cent of the allergic infants developed major allergic symptoms during the course of this observation in spite of early diagnosis and prophylactic treatment. These allergic diseases were of varied nature; perennial allergic rhinitis was most frequent, followed by hay fever (pollinosis), asthma, eczema, gastro-intestinal allergy, hives, and a few other less common conditions. Several of the above were often associated at one time or another in the allergic cycle in the child.

4. Only one allergic symptom in a child occurred in 56 per cent of the cases. Perennial rhinitis was the only major allergic symptom in 26 per cent, pollen hay fever in 17 per cent, asthma in 6 per cent, and eczema in 7 per cent. Other children had multiple symptoms.

5. The first allergic symptom in infancy does not usually determine the type of allergy that will develop later.

6. Most cases of major allergy developed before six years of age; only 15 per cent in this series occurred after six years of age.

7. Perennial allergic rhinitis occurred most often as the first major allergic symptom. Hay fever, asthma, hives, and gastro-intestinal symptoms develop as the first form of allergy more often than is generally recognized.

8. Prophylactic treatment, advocated early and thoroughly, did not pre-

vent the development of major allergy as the child grew older. Ninety-eight of 100 children developed symptoms of major allergy. The preventive treatment probably minimized the course of the disease and its complications. Children adequately treated for allergic disease grow and develop physically the same as normal children.

9. Treatment was that of the pediatric allergist. The child was treated primarily as a pediatric problem with the aid and refinements of allergic technique.

#### CONCLUSION

This ten-year study has shown that with our present knowledge we cannot prevent the development of major allergic disease in infants who have an inherent allergic constitution. It is discouraging to know that, although we are able to diagnose the allergic state in the first few months of life, the infant will almost inevitably develop major allergic symptoms in his early childhood. Prophylactic treatment, in its present state of development, will probably minimize or ameliorate the allergic symptoms, allowing the child to grow and develop normally, both physically and mentally.

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MYOCARDITIS IN BRONCHIECTASIS. Saphir, Otto: *Arch. Int. Med.*, 72: 775, (Dec.) 1943.

It is noted that myocarditis is associated relatively more frequently with bronchiectasis than with uncomplicated pneumonia. Clinical data on eight patients (among 152) with bronchiectasis and associated myocarditis are presented. The most significant clinical observation is the discrepancy between the relatively slight elevation of temperature and the high pulse rate. At autopsy, two patients had hearts of normal size, six presented right ventricle hypertrophy. The myocarditis was diagnosed not by gross examination but histologically. There was recent myocarditis in five cases, subacute and chronic in one each. The cause of myocarditis very likely was a primary focus of bronchiectatic infection. It is suggested that a careful study of the myocardium in bronchiectasis and bronchial asthma may discover or rule out myocarditis before reporting negative result. It may occasionally account for sudden deaths.

L.J.H.

# PROBLEMS IN THE DIAGNOSIS OF BRONCHIAL ASTHMA

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THE diagnosis of bronchial asthma is not difficult. Yet even experienced allergists are confronted practically daily with certain diagnostic problems. Some of these problems have been thoroughly dealt with in the literature, whereas others have been neglected. On some, statistics are available, but the issues at hand are not as yet clear. These questions will be discussed as follows: (1) Certain features concerning the differential diagnosis; (2) some diseases occurring simultaneously with bronchial asthma; (3) the common complications; (4) some rare complications of allergic asthma which may or may not have an etiological relationship to this disease.

## DIFFERENTIAL DIAGNOSIS

The fact that all lung diseases and some extrapulmonary thoracic conditions may be accompanied by wheezing and dyspnea and thus may camouflage the clinical picture of bronchial asthma, formerly has accounted for a great deal of confusion. Even now, we find occasional autopsy reports in which the distinction of true bronchial asthma from nonallergic wheezing has not been carried out. It is not necessary to dwell on this question here. However, a common fallacy to which the more experienced allergist is often subject should be emphasized. In our endeavor to make the correct diagnosis, we sometimes fail to realize that such disorders as cancer of the lungs, foreign body in the lungs, a syphilitic heart, pulmonary abscess—in other words, conditions which produce considerable wheezing—may occur simultaneously in patients with allergic asthma. Their presence does not justify neglect of the patient's allergic state.

Concerning the differential diagnosis, a few points should be brought out which are usually not sufficiently stressed in textbooks: If wheezing is localized in a certain pulmonary area instead of being equally distributed throughout the lungs, one should always consider the possibility of a non-allergic process. If râles are present in addition to asthmatic bruits, some disease other than allergic asthma or some of its complications should be suspected, usually pneumonitis or bronchiectasis. A simple sign, sometimes helpful in establishing the diagnosis, is the observation of the patient's position. When an "asthmatic" patient is lying down, he should be suspected of having some other disease. Some of us have utilized, as a diagnostic criterion, the patient's response to epinephrin. This cannot be accepted without reservation. Not all allergic asthmatic patients respond to epinephrin and, conversely, patients with nonallergic wheezing obtain relief from it occasionally. When allergic asthma is complicated by pneumo-

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Fig. 1. (left) Case 1. Miss J. B., thirty-four years old. Partial obstruction of main bronchus in pulmonary tuberculosis simulating asthma. Note distention above the constricted area, visible after lipoidal injection.

Fig. 2. (right) Case 2. Mrs. B. L., thirty years old. Small area of active tuberculosis in left apex of two weeks' duration in an allergic asthmatic patient.

nitis, epinephrin is of little value. When there is doubt concerning the diagnosis, a most reliable feature in the patient's history is the question of whether or not nasal symptoms have been present before, or are associated with, the asthmatic condition. If we fail to obtain this history, we should be skeptical about making the diagnosis of allergic asthma.

#### COINCIDENCE OF ASTHMA WITH OTHER DISEASE

It is assumed today that the allergic wheal is liable to occur in practically any part of the system. Therefore, any ailment occurring simultaneously with asthma should be scrutinized as being etiologically related to it. There are two diseases which have been said to occur very rarely in association with bronchial asthma; namely, diabetes and tuberculosis. Thyroid diseases and heart disturbances, on the other hand, have been identified as occurring more frequently in the asthmatic than in the average individual.

The question of diabetes (Beckman<sup>1</sup>) can be easily disposed of, as all of us have not only seen this combination, but are quite familiar with the occurrence of sensitivity to insulin, which so often aggravates existing allergic asthma. I had occasion to observe the reverse relationship—namely, that an asthmatic state lowered the sugar tolerance.

The question of tuberculosis is more complex. Some German clinicians stated that these two diseases could not occur simultaneously, while others held that asthma originated from tuberculosis. The literature has been well



summarized recently by Tooker and Davidson.<sup>5</sup> Through co-operation with several tuberculosis specialists in Detroit, I have had an opportunity to observe a rather large group of cases presenting the combination of tuberculosis and asthma. This experience has brought out the following facts:

1. Asthmatic wheezing is encountered during the course of tuberculosis and is easily confused with asthma. Enlarged tubercular glands, strictures of bronchi, mucus and caseous material lodged in the bronchial tubes may induce bronchospasm and considerable wheezing in patients who are not allergic. Figure 1 (Case 1, Miss J.B., thirty-four years old) illustrates a bronchial stricture of tuberculous origin. Wheezing remained the most conspicuous manifestation at a time when the healing of the tuberculosis had progressed very satisfactorily.

2. Allergic asthma may become complicated by tuberculosis. This has been rare among my patients. That it does occur is illustrated by Case 2 (Mrs. B. L., thirty years of age) a patient with allergic asthma, who developed what appeared to be an upper respiratory infection with temperatures ranging up to 101 degrees. When she failed to improve promptly, the x-ray (Fig. 2) revealed a very small acute tubercular focus. This was associated with positive sputum.

3. Tuberculosis may be followed by allergic asthma. This, as well as hay fever, in the tuberculous patient is not uncommon. In treating these patients with pollen extracts, generalized reactions should be carefully avoided as they may induce the flare-up of the tuberculous lesions.

4. In three asthmatic patients with healed tuberculosis, I have observed strong skin reactions to tuberculin while the usual skin tests for allergy were not conclusive. Although there was a typical background of allergy, they had not responded to the usual allergic management. Upon instituting tuberculin treatment (Van Leeuwen<sup>8</sup>) with very small doses, these patients were completely relieved of asthma. They may have been primarily sensitive to tuberculin.

There is a strong feeling among some clinicians that hyperthyroidism plays a part in the asthmatic state. This is evidenced by the frequency with which these patients are subjected to metabolic studies. Indeed, the fast pulse, so commonly encountered during asthmatic attacks, the existing emaciation, often accounted for by sudden loss of fluid, may lead to this belief. Others have associated a low metabolic rate with asthma. Systematic metabolism studies on a large group of asthmatic patients have been carried out by some, but never published, evidently because they yielded no deviation from the normal state. On several occasions I encountered asthmatic persons whose disease responded very promptly to thyroid medication and others to the removal of a hyperplastic thyroid. Such an instance is Case 3 (Mr. J. S., fifty-three years of age), who had been in an extreme, chronic, asthmatic state. He was sensitive to many antigens. He

had taken large doses of epinephrin. His asthma failed to improve from allergic management, but cleared up promptly upon thyroidectomy.

There has been some controversy as to whether or not an asthmatic patient is more likely to develop a heart disease than a normal individual. Two symptoms which are very pronounced in practically every asthmatic person have led to speculation on this possibility—namely, the occurrence of dyspnea upon the slightest exertion, and the presence of a fast pulse. In interpreting some of the statistical material available, which is summarized by Urbach<sup>7</sup>, we should be aware of the following facts: Heart disease is a very common disease. If present in an asthmatic person, the enlarged heart may, through pressure on the air passages, contribute to the asthmatic wheezing. This effect may be enhanced by existing pulmonary congestion from cardiac decompensation. Moreover, the continued use of such drugs as ephedrin and epinephrin in asthma may lead to cardiac damage. That allergic asthma will lead to significant changes in the heart, is unlikely for the following reasons: (1) In the average asthmatic person such manifestations as nycturia, edema, enlargement of the liver, are rare. (2) The typical x-ray study of a patient with asthma, even though it be of years' standing, does not show an enlargement of the heart. (3) The electrocardiographic changes noted in asthmatic persons (Harkavy and Romanoff<sup>8</sup>) are not impressive and may disappear after the subsidence of the attack. This is in line with the cardiac findings at autopsy in asthmatics (Lamson et al.<sup>4</sup>) which occasionally reveal acute dilation of the right heart, but no changes indicative of *chronic* disease.

#### COMMON COMPLICATIONS OF ASTHMA

The three common complications of allergic asthma are sinus disease, pneumonitis, and bronchiectasis. A proper evaluation of the condition of the sinuses, as well as of the tonsils, in allergic diseases is of great importance because of its therapeutic aspect. Enlarged tonsils, waterlogged nasal membranes, septum deviation, enlarged turbinates, and cloudy sinuses are generally accepted as resulting from the asthmatic state rather than causing it. Nevertheless, much remains to be clarified as to whether these structures should be treated surgically. Our greatest fallacy, I believe, is the undue stress of, and reliance on, such features as the presence or absence of eosinophil cells in the nasal mucus, the occasional findings of pus and cloudiness on transillumination or on x-ray evidence in the sinuses. There are two indications for a nasal operation in asthma: (1) chronic suppurations and chronic empyema of the sinuses; (2) continued interference with ventilation of the nose and drainage of the sinuses. In either case emphasis should be placed on chronicity and on the fact that a previous attempt at allergic management has failed to bring about a noticeable improvement. Also, concerning the indication for tonsillectomy in asthmatic persons, further clarification is needed. It has been demonstrated repeatedly that tonsillectomy may be followed by con-

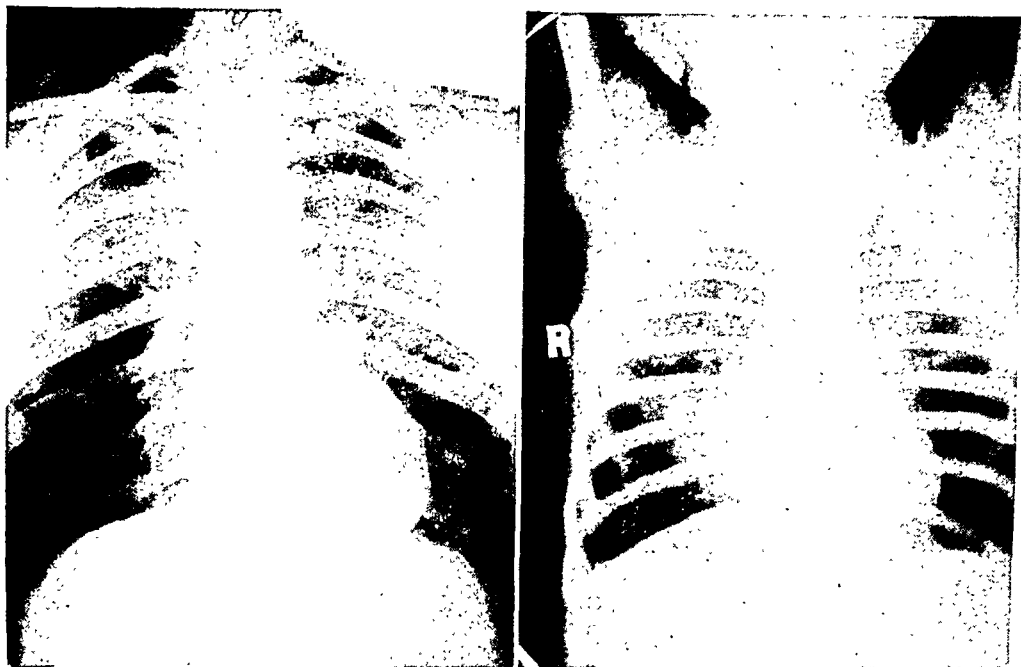


Fig. 3 (left) Case 4. Mr. V. B., thirty-five years old. Low-grade pneumonia, probably from allergic pulmonary edema, occurring suddenly through inhalation of pigeon feathers.

Fig. 4. (right) Case 5. B. W., two years old. Pneumonitis (chronic) in right lower lung, resulting from obstruction of a bronchus by mucus.

siderable aggravation of the asthmatic state. According to our own statistical studies<sup>10</sup>, not only the asthma fails to be relieved, but also other conditions for which the operation is performed, such as arthritis and ear infections, improve less readily than in nonallergic individuals. In other words, what appears to be infected tonsils and cervical glands, may actually represent waterlogged, edematous, hyperplastic lymphoid tissue superseded by secondary infection, changes corresponding to the condition of the mucous membranes of sinuses and bronchi. However, we should not accept these facts dogmatically. I observed several patients with enlarged tonsils whose asthma was refractory to any treatment until the tonsils were removed. It has been my practice to advise tonsillectomy, if there is a history of *frequent* febrile tonsillitis and if the clinical course of asthma indicates that we are dealing with an infectious type of asthma rather than with primary sensitivity to the common antigens. The morphological appearance of the tonsils or adenoids matters little in the indication for the operation.

During the course of allergic asthma, various types of pneumonitis are encountered, the proper clinical evaluation of which may present great difficulties.

1. There is the usual infectious type of pneumonia brought on by the common organisms of the disease. Whether or not its course is more violent and fulminating than that in a normal individual is difficult to state.

2. In asthma of short duration, especially in infants and young children,

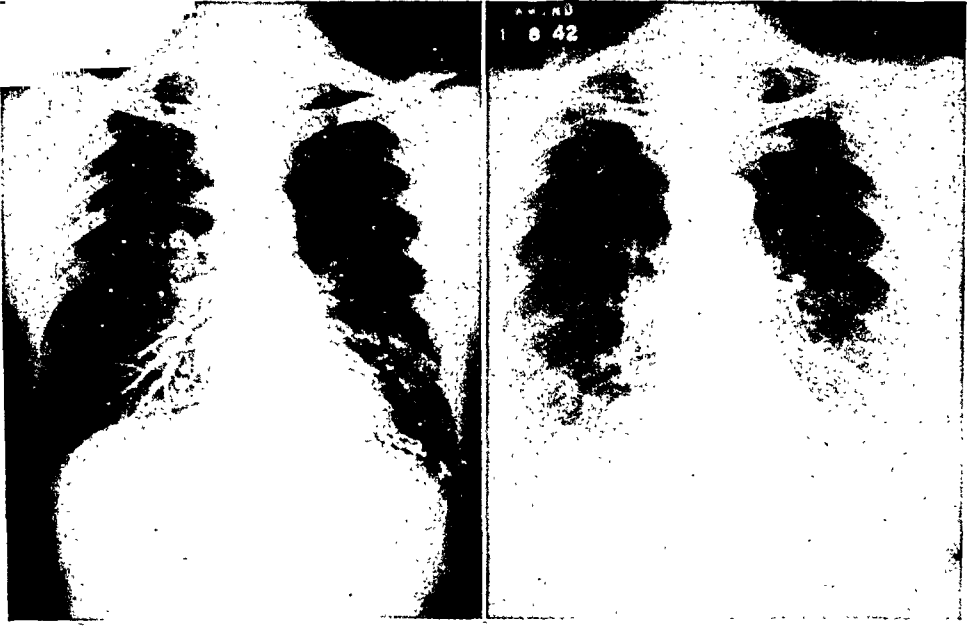


Fig. 5. (*left*) Case 6. Mr. A. S., thirty-four years old. Extensive saccular bronchiectasis confined to left lower lobe in a hay-fever patient, probably a congenital process causing no symptoms other than some cough in the morning.

Fig. 6 (*right*) Case 7. Mrs. H. W. H., seventy-five years old. Atelectasis of right lower lobe in an allergic asthmatic.

a certain type of pneumonitis occurs which can be regarded as a part of the clinical picture of the asthmatic attack (Waldcott<sup>9</sup>). This is the "pneumonia" which the patients relate in their history as having brought on the first attack of asthma. It is an allergic edema which becomes infiltrated with leukocytes after several hours. It is best illustrated by Case 4 (Mr. V. B., thirty-five years of age), who had always been in perfect health. On entering a pigeon coop he suddenly developed a cough, wheezing, and pronounced shock (Fig. 3). This was followed, after six hours, by moderate temperature lasting for three days. This episode was the beginning of a long course of asthma, primarily due to pigeon feathers. In another case, described elsewhere in detail<sup>9</sup>, a child developed shock and fever shortly after ingestion of milk. The pathological section from the lungs of this patient illustrates how small areas of edema become infiltrated with leukocytes at their periphery.

3. Some assume that atelectasis resulting from obstruction of small bronchi with mucus might account for secondary pneumonitis, the obstructed areas becoming subsequently infected. This mode of pneumonitis is demonstrated in the x-ray (Fig. 4) of a two-year-old girl (Case 5, B.W.) with allergic asthma. A mucous plug obstructed a large bronchus, accounting for fever and consolidation in this area for several months. This condition cleared up promptly upon removal of the mucus bronchoscopically and upon dilatation of the resulting scar in the bronchus. While the involvement of such a large pulmonary area as in this case is relatively

rare, smaller lesions from obstructed secondary bronchi are frequently encountered during asthmatic attacks.

4. Through the investigation of Harkavy<sup>2</sup> and others, the so-called "Loeffler's syndrome" has been given general attention, a pneumonialike infiltration characterized by fever, high leukocytosis, and high eosinophilia. The lesions are transient, occurring in various parts of the lungs at different times. It is thought that this condition may originate from allergic reactions in capillary vessels in the lungs.

We need not dwell at length on bronchiectasis. There are two types, the cylindrical and the saccular. The latter type is rare and, as in Case 6 (Mr. A. S., thirty-four years of age), might represent a coincidence with asthma (Fig. 5). Even extensive bronchiectasis is not always as hopeless as it appears to be. I have seen many such patients improve considerably from allergic management in conjunction with bronchoscopic lavages. It is likely that small bronchi, which are greatly dilated and have been filled with mucus and pus during the course of a long-standing attack, can regain their normal elastic state after the pus has been removed and is prevented from reappearing.

#### RARE COMPLICATIONS OF ASTHMA

The following three cases are, I believe, rare complications of bronchial asthma—namely, atelectasis of a whole pulmonary lobe, cystic degeneration of the lungs, and multiple, spontaneous fractures of the ribs. It is possible that these manifestations may be coincidental. Others (Tuft<sup>6</sup>)\* have encountered massive atelectasis as sequelae of asthma.

*Atelectasis of Pulmonary Lobe.*—Mrs. H. W. H., aged seventy-five (Case 7), had had allergic asthma since the age of seventeen. The attacks were usually preceded by allergic rhinorrhea and by upper respiratory infection. There was no tendency to seasonal aggravation.

About two months ago a severe asthmatic attack occurred during which she became pulseless and extremely short of breath requiring constant attention by her physician for five hours (heart stimulants, oxygen, and aminophyllin). Since then, the dyspnea and extreme cyanosis were present continuously.

Examination showed a well-developed, well-nourished female with marked dyspnea and cyanosis. There was physical evidence of marked asthma; there was x-ray evidence (Fig. 6) of complete atelectasis of the right lower lobe of the lung. In addition there was tortuosity of the aortic knob, pleural thickening over the apices, and a few calcified nodes in the hilus and in the parenchyma of the right lung. Particular attention was paid to ruling out a neoplasm and a heart disease by subsequent x-ray examinations. After one month the persistence of the atelectatic lobe was still evident, but another check, two years later, showed normal lungs.

\*Spontaneous rib fractures were reported to me orally by several clinicians viewing my AMA exhibit, 1940.

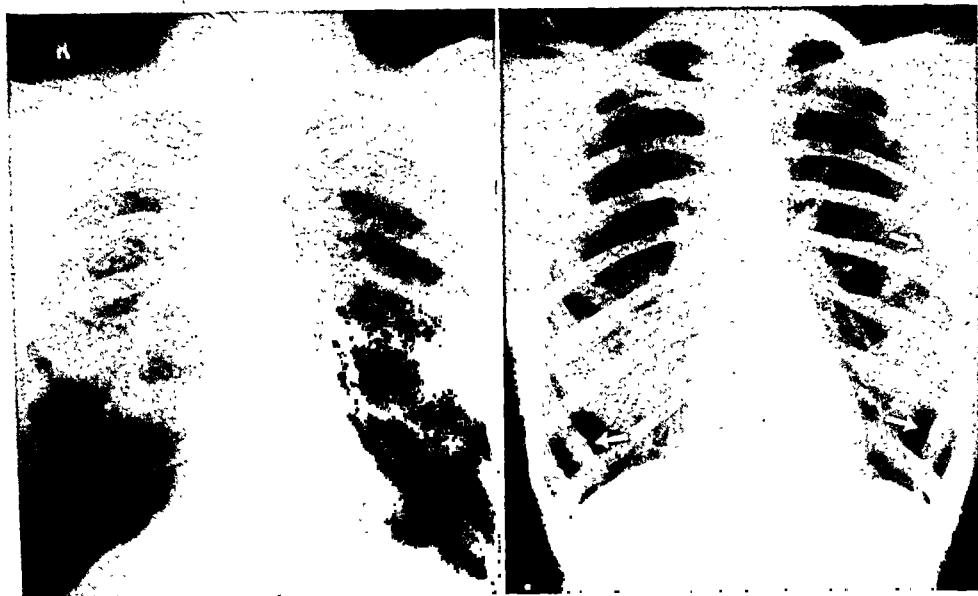


Fig. 7. (left) Case 8. Mr. L. A., fifty-three years old. Cystic degeneration of lungs (ruptured alveoli) in a chronic asthmatic patient. Ten years previously the patient had a left-sided spontaneous pneumothorax. Note air blebs especially in lower portions of lungs.

Fig. 8. (right) Case 9. Mrs. E. C., thirty years old. Spontaneous rib fractures in a case of chronic allergic asthma.

The asthma responded very well to allergic management. The patient refused bronchoscopic aspiration which was indicated. Atelectasis of a whole lobe may well be brought about by obstruction of the main bronchus.

*Cystic Degeneration of Lungs.*—Mr. L. A., fifty-three years old (Case 8), had had allergic asthma since the age of twelve. Up to 1925 the attacks had occurred intermittently, mostly in summer and fall. During later years they were continuous. In May, 1932, the patient experienced a sudden collapse and severe pain in the left side radiating into the apices. At that time the x-ray revealed advanced emphysema and a left-sided pneumothorax. Complete intradermal skin tests had shown positive reactions to a large group of antigens, especially to ragweed and house dust.

On examination, in 1941, the patient showed extreme emaciation with great respiratory distress. The chest was barrel shaped. There was little expansion. Wheezing and coarse râles were heard throughout the lungs. Heart sounds were distant. X-ray examination (Fig. 7) showed extensive bilateral emphysematous changes with multiple large emphysematous bullae.

It may be assumed that during the years of severe cough and dyspnea, the patient "blew out" an emphysematous area near the periphery of the left lung, first causing a pneumothorax and later a cystic degeneration of the lungs. Both pneumothorax and ruptured alveoli have been seen in other patients with allergic asthma.

## DIAGNOSIS OF BRONCHIAL ASTHMA—WALDBOTT

*Multiple Fracture of Ribs.* Mrs. E. C., thirty years old (Case 9), had had asthma since the age of nine. The asthma was originally precipitated by ragweed hay fever. Four months before I saw her, the patient experienced severe coughing spells during which extreme pains in various parts of the ribs were noted.

The physical examination revealed nothing significant other than considerable emaciation (90.5 pounds) and typical asthma throughout both lungs, cloudy sinuses and evidence of fractured ribs.

The x-ray examination showed four rib fractures in different stages of healing. Blood studies and bone marrow puncture were performed to rule out certain hematological diseases and metastatic tumors. They were negative except for a 10 per cent blood eosinophilia. Calcium and phosphorus levels of the blood were normal.

The spontaneous rib fractures were probably due to intense coughing during an attack.

### SUMMARY

1. Various features in the differential diagnosis of bronchial asthma are emphasized.
2. The association of asthma with other allergic and nonallergic conditions is reviewed.
3. Common and some rare complications of asthma are related.

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### SUCCESSFUL TREATMENT OF EXTREME ALLERGY TO BEE BODY AND BEE VENOM. McLane, E. G., *Minnesota Med.*, 26:1061, (Dec.) 1943.

McLane reports a case in which marked sensitivity to bee body and bee venom was overcome by graduated injections of whole bee extract, followed by carefully spaced bee stings. Inasmuch as this extract protected the patient from both bee emanations and stings, the author suggests that there is a common substance present in both allergic sources. Bibliography.

W.J.H.

## UNUSUAL COMPLICATIONS OF BRONCHIAL ASTHMA: AIR IN EXTRA-PULMONARY SPACES

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THERE are few acute clinical manifestations which are more distressing and dramatic to the physician and patient alike than the asthmatic paroxysm to which is added the consequences of pulmonary rupture. The course taken by the liberated air determines whether there will be subcutaneous emphysema, spontaneous pneumothorax, mediastinal emphysema, or a combination of any of these. Blood vessels, fibrous tissue and old adhesions are among the factors which direct the escaped air. Over the past year we have seen a number of asthmatic patients who suffered such complications. From this series we have selected instances which represent the typical course of events.

### SPONTANEOUS PNEUMOTHORAX

Although pneumothorax is generally considered to be a complication of pulmonary tuberculosis, it is the opinion of phthisiologists<sup>11</sup> of wide experience that tuberculosis is the etiologic agent in not over 10 per cent of the cases. In view of the marked thinning of the alveolar walls and increase in intra-alveolar pressure so often present in chronic asthma, it might be assumed that spontaneous pneumothorax will occur frequently in this condition. In a survey of the literature in this regard, we<sup>2</sup> find only about twenty-one such instances.

Detailed discussion of these serves little useful purpose because of their great similarity. One of our patients was a forty-eight-year-old white man who was suddenly seized with an attack of severe dyspnea and orthopnea. In addition to the presence of sibilant râles, findings on physical examination indicated displacement of the heart and trachea to the left. The patient died on the fourth hospital day, and autopsy revealed collapsed blebs at the apex of the right lung in addition to the pneumothorax.

Classically, in these patients, the findings differ little from those seen in uncomplicated pneumothorax except that, if the complication occurs during the asthmatic seizure, the characteristic signs of bronchial asthma are superimposed. Among the outstanding symptoms are pain, dyspnea, cough and collapse. Typically, on physical examination, there is a decrease in fremitus, breath and voice sounds. As in the reported instance hyperresonance to percussion can be demonstrated together with dis-

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placement of the heart and mediastinal structures to the unaffected side. Roentgen examination confirms the physical findings and in many instances reveals small degrees of pneumothorax which would otherwise be overlooked.

#### MEDIASTINAL EMPHYSEMA AND SUBCUTANEOUS EMPHYSEMA

Although mediastinal emphysema was first described by Mueller in 1888<sup>8</sup>, it received little notice until 1937 when Hamman<sup>4</sup> directed attention to it.

Because individuals having chronic asthma are frequently in the age group liable to have coronary artery disease, a particularly perplexing differential diagnostic problem may arise when this condition occurs with asthma. Indeed, in Hamman's first case the patient, a physician, was thought to have myocardial infarction; only later, when air was discovered in the anterior mediastinum, was the correct diagnosis established.

One of our patients was seen in the admitting room of Charity Hospital with the chief complaints of asthma and substernal pain. On examination the findings, which are now recognized as classical of mediastinal emphysema, were elicited. Later, in the ward, swellings in either side of the neck were detected. Examination revealed the pathognomonic crepitations of air in the subcutaneous tissues. The outstanding finding of mediastinal emphysema is a peculiar loud, crackling, bubbling sound which is synchronous with the heart beat. As Hamman and others have observed, we too on occasion have been able to hear this crunching noise at some distance from the patient without the aid of the stethoscope. Although it has been emphasized that this condition may occur without the least effort and regardless of the position of the patient, it will readily be appreciated that severe respiratory muscular imbalance will precipitate the syndrome.

The entrance of air into the mediastinum with forceful separation of those structures results in substernal pain not unlike that found in myocardial infarction. It is well known that severe pain is not a part of the asthmatic picture, and its presence therefore should immediately direct the attention of the attending physician to some complication. As Hamman<sup>4</sup> has pointed out, there are negative points of great value in making the diagnosis. These are an absence of constitutional symptoms and of evidence of shock, a normal temperature, and lack of change in blood pressure and leukocyte count. On physical examination, the area of cardiac dullness may be replaced by one of resonance to hyperresonance.

It is well to emphasize that even in the absence of the typical physical findings the presence of air in the mediastinum can be demonstrated roentgenologically. In the above case the pneumothorax which was present was small and could be detected only by roentgen-ray study.

The air which has accumulated in the intrapleural space works its way, as Macklin<sup>7</sup> has shown, along the sheaths of the blood vessels and the fascial planes until it reaches the hilus and in this manner finds its way into the anterior mediastinum where it is later absorbed. This is the usual sequence of events, however, as in our case, the air may subsequently work its way along fascial planes following the course of blood vessels and make itself known as subcutaneous emphysema about the base of the neck.

Subcutaneous emphysema is a rare complication of bronchial asthma as shown by the fact that a late review of the subject<sup>9</sup> brought to light only eighteen cases from the world literature. Clinically, subcutaneous emphysema may involve not only the neck but may extend to the face, upper extremities, thorax, and abdomen, but only rarely does it involve the thighs. From the reported cases, it would appear that subcutaneous emphysema carries a good prognosis. To our knowledge, no deaths have been reported, and there have been no recurrences in spite of the fact that patients were subjected to further attacks of bronchial asthma. The condition is self-limited, and in from four days to two weeks recovery is usually complete. Most of the patients were young and distributed equally between the sexes.

#### DISCUSSION

Although emphysema is one of the most common complications of bronchial asthma, it is indeed interesting to note that pneumothorax occurs very rarely. It would appear that the thin avascular alveolar wall would be a perfect site for a laceration of lung tissue.

It might be well to point out that tension sufficient to produce rupture of the normal pleura does not result from even the most severe paroxysms of coughing, unless there is some anatomic or pathologic alteration, either congenital or acquired. West<sup>10</sup> showed half a century ago that the normal pleura cannot be ruptured unless the intrapulmonary pressure exceeds 200 millimeters of mercury. It is paradoxical that rupture does not occur more frequently in emphysema, for Zahn<sup>12</sup> has shown that normally the alveolar wall plus the visceral pleura measures 0.13 to 0.24 mm., whereas in emphysematous lungs the thickness may diminish to as little as 0.03 mm.

The explanation of Castex and Mazzei<sup>1</sup>, that in emphysema a progressive decrease in the negativity of the intrapleural pressure occurs so that finally this pressure approaches positive, and in this manner an equilibrium is established between the intrapleural and intra-alveolar pressures, is in our opinion the most logical explanation for the rarity of rupture of the blebs which occur so uniformly.

There are forces at work, however, which tend to disturb this attempt of the body to maintain homeostasis. We feel that regardless of the

cause, be it tuberculosis, congenital cyst, or an emphysematous valve vesicle, the rupture occurs through the intermediary of a valve vesicle. As Kjaergaard<sup>6</sup> and Hyoshi<sup>5</sup> have shown by postmortem studies, this



Fig. 1. Enlarged roentgenogram demonstrating the valve vesicle and partial pneumothorax.

valve vesicle actually occurs, and with each inspiration more air enters the vesicle than leaves it. In this manner, a sequence of events is established which allows for stretching and finally rupture of the vesicle. In Figure 1 (courtesy of Dr. J. L. Wilson), such a vesicle may be seen.

It has been pointed out elsewhere that there is greater danger of rupture on deep inspiration than following a paroxysm of coughing. In coughing, the tendency is for closer approximation of the lung to the chest wall. This results in a lessening of the positive pressure in the alveoli and a decrease of the negative pressure in the intrapleural space. Following a deep inspiration there is atmospheric pressure in the alveoli and a decrease of the negative pressure in the intrapleural space. Following a deep inspiration there is atmospheric pressure in the alveoli and negative pressure without, favoring rupture. We believe that the reason why spontaneous pneumothorax is not more frequent in bronchial asthma is that the expiratory element is definitely prolonged at the expense of inspiration.

It is well to point out, however, that in the pneumothorax which followed mediastinal emphysema, Macklin was unable to demonstrate a tear in the visceral pleura, but could show a definite tear in the mediastinal wall. As Hamman has shown, we must at least entertain the possibility

that the initiating lesion for the pneumothorax may be the escape of air into the pleura from the mediastinum. There are reports of cases of this nature showing a fine sharp line running parallel to the border of the



Fig. 2. Note fine sharp line running parallel to left border of heart.

heart on roentgen examination. We have had occasion to observe a similar instance, the roentgenogram of which is shown in Figure 2.

The outlook for patients with these complications of bronchial asthma is extremely good indeed. There is little doubt in our minds but that all these conditions, especially pneumothorax, occur much more frequently than is suggested by the literature.

As we have mentioned elsewhere, the physician should exercise restraint in the use of mechanical measures because the nature of the lesion is such that with little or no treatment the great majority of the patients completely recover. We should like especially to emphasize the dangers associated with tap of the pleural space and removal of the escaped air. This practice disturbs a protective mechanism—namely, the equality of pressure on either side of the alveolus. This pressure equality allows for a minimum of movement and maximum healing. Removal of air, then, sets into motion forces which lead to bronchopleural fistula and which may not only result in a tension pneumothorax but in a contaminated pleural cavity as well.

We feel that bed rest for about a month and sedatives as needed are the most important points in the treatment, and that thoracentesis should be reserved for those cases of tension pneumothorax where the intrapleural pressure is such as to embarrass seriously the patient's respiration.

Once healing has been accomplished, the nitrogen factor of the escaped air, which is still in the pleural spaces, may be absorbed more rapidly by the use of oxygen in a concentration approaching one hundred per cent. Fine<sup>3</sup> and his group, using this method, have been able to increase the diffusion pressure of the nitrogen between the pleural space and the blood vessels and in this manner bring about a more rapid absorption of this gas.

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PERIARTERITIS NODOSA; REPORT OF CASE. Lichtman, A. L., Stickney, J. M., and Kernohan, J. W.: *Proc. Staff Meetings of Mayo Clinic*, 18:500, (Dec. 15) 1943.

An illustrative case report. Histogenically, in periarteritis nodosa, there is necrosis of media with resulting extension of inflammatory reaction and repair into perivascular tissues. The subsequent infarction produces disability. Marked variation of vascular involvement is outstanding characteristic. Occlusion of vasa nervosum has been a constant observation of authors. Eosinophile cells are usually present in the inflammatory reaction. The symptoms vary with the degree of involvement of different organs and tissues, depending on the interruption of the blood supply. Asthma (in 15 to 20 per cent) eosinophilia (often 70 to 80 per cent), and peripheral nerve involvement are common characteristics of periarteritis nodosa. The etiology is probably allergic or infectious with neither definitely proven. L. J. H.

**POLLINOSIS IN SAN DIEGO COUNTY, CALIFORNIA**  
**With a Proposed Method for the Estimation of the**  
**Relative Importance of the Plants Concerned**

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**M**OUNTAINOUS areas such as Southern California present a great diversity of topography and vegetation. To a large extent, the centers of habitation are surrounded by mountain ridges which act as more or less effective barriers to air-borne pollens so that each community is a problem in itself. The multiplicity of potential causes of pollinosis in such an area renders it necessary to determine as accurately as may be the significance of each of the plant species found.

Numerous authors have reported pollen counts and botanic surveys for various communities throughout the world. A review of the available literature revealed the astonishing fact that in none of these was all the necessary data given to evaluate quantitatively the actual or relative importance of the individual plant specimen involved, nor was any method or formula suggested for arriving at a quantitative expression for the over-all importance of each species after consideration of the various factors involved.

In rare instances in which the pollen of the individual species can be identified microscopically, pollen counts at suitable stations are adequate, but for all others field studies are necessary. It would seem indisputable that the importance in pollinosis of a given pollen species with respect to a given patient would be mathematically the product of the degree of the patient's sensitivity to that pollen and the amount of it to which he is exposed. It would also seem self-evident that the amount of pollen to which the patient is exposed can be expressed as the mathematical product of the abundance of the species, the amount of pollen produced in a given time per unit area, the period of pollination, and some factor which expresses the ability of the pollen to travel from the plant to the patient. Any quantitative evaluation must necessarily be an approximation since there are many variable factors such as the proximity of the plants to centers of habitation, the prevailing direction and velocity of the wind, the height from which the pollen takes off in its travel through the air, the existence of spicules or wings on the pollen, and, of course, the changing location of the patient himself. The toxicity of the pollen species varies with each patient but is determined roughly by skin testing.

The existence of these variable factors does not excuse us from trying to be as accurate as possible. It seemed desirable, therefore, to adopt some scheme which would bring into their proper relationship all of the factors which are susceptible of quantitative evaluation.

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To this end we deliberately assumed as a standard, a hypothetical plant with a pollinating period of two months, a pollen diameter of 25 microns, a pollen production of 100, and an abundance of 10 on a scale of 1 to 10. To this hypothetical plant we assigned an importance rating of 100. It was assumed that the buoyancy of a pollen of a given size would be inversely proportional to the velocity of its fall in air. The velocity of fall in air at 20° C. for pollen of various sizes is given by Dahl and Ellis\*<sup>3</sup> who based their calculations on Stokes' formula.†<sup>7</sup> Hence the buoyancy factor may be determined by dividing the velocity of fall of a pollen of 25 microns diameter by the velocity of fall of the pollen in question. The pollen production of *Franseria acanthicarpa* (false ragweed) was assigned a rating of 100 because this species, among the plants in our locality, most closely resembles *Ambrosia elatior* (dwarf ragweed) which has been assigned a value of 100 by several other authors. Barrett,<sup>1</sup> in Salt Lake City, found it to have a pollen production value in that area of 65 as compared to 100 for *Ambrosia elatior*. The actual pollen production of *Franseria acanthicarpa* was found to be 1.7 gm. per day for one square meter of a pure stand when collected at the peak of pollination.

The importance rating of any given species may be determined with respect to this hypothetical plant by the following formula:

$$\frac{n}{2} \cdot b \cdot p \cdot \frac{a}{10} = \text{I.R.}$$

where

- n = number of months of pollination  
 b = buoyancy factor  
     =  $\frac{\text{velocity of fall of a pollen of } 25\mu \text{ diameter}}{\text{velocity of fall of the pollen in question}}$   
 p = pollen production (*Franseria acanthicarpa* = 100 = 1.7 gm./day/sq. meter)  
 a = abundance (scale of 1 to 10)  
 I.R. = importance rating

\*The following is taken from the tables of Dahl and Ellis<sup>3</sup>:

Diameter of pollen grains in microns	Velocity of fall (feet per second)
15	.022
18	.032
22	.048
25	.062
28	.078
32	.102
36	.129
40	.159
44	.192
48	.229
50	.248

\*Example: *Lolium multiflorum* (Italian ray grass) (See Table IV, p. 36)

$$n = 5; b = \frac{.062}{.129}; p = 105; a = 4$$

$$\frac{5}{2} \times \frac{.062}{.129} \times 105 \times \frac{4}{10} = 52$$

†Stokes' formula:  $V = \frac{2 \text{ gr}^2 (d_1 - d_2)}{9 K}$

where

V = velocity in cm./sec.

g = acceleration of gravity = 980 cm. per sec.

r = radius of the sphere

d<sub>1</sub> = density of the sphere

d<sub>2</sub> = density of the medium

K = coefficient of viscosity of the medium (air at 20° C. to 23° C.) = 0.00018

# POLLINOSIS—HARSH ET AL.

TABLE I. TOTAL POLLEN GRAINS FOUND ON ONE SQUARE INCH OF SLIDE  
FOR ONE YEAR

	San Diego 1936-1941 (average)	Escondido 1936	Alpine 1936
Cupressus and Juniperus (cypress and juniper)	2921	1607	648
Gramineae (grass)	1320	1451	1342
Artemisia (sagebrush)	1073	2708	2094
Quercus (oak)	978	3104	40719
Chenopodiaceae and Amaranthaceae (goosefoot and pigweed)	456	414	1829
Ambroseae (ragweed)	452	404	1137
Adenostoma and Eucalyptus (chamise and eucalyptus)	371	499	566
Palmaceae (palm)	339	14	0
Schinus (pepper tree)	231	364	54
Olea (olive tree)	162	391	303
Other compositae (other than sagebrush and ragweed)	152	340	467
Platanus (sycamore)	51	89	50
Juglans (walnut)	39	205	37
Populus (cottonwood)	36	45	248
Alnus (alder)	35	20	185
Acacia (acacia tree)	35	48	4
Salix (willow)	14	222	240
<b>Gramineae</b>	<b>1941</b>		
Under 30 microns diameter	954		
31-40 microns diameter	672		
41-50 microns diameter	134		
over 50 microns diameter	27		

TABLE II. GRASS POLLENS GROUPED ACCORDING TO SIZE OF THEIR GRAINS

	Pollinating Period (months)	Importance	Pollen Size
<b>Over 50 microns diameter</b>			
Avena fatua (common wild oats)	2-4	10	53
<b>41 to 50 microns diameter</b>			
Spartina leiantha (cord grass)	6-9	4	47
Sorghum halepense (Johnson grass)	5-9	7	43
Bromus rigidus (broncho grass)	4-5	20	43
<b>31 to 40 microns diameter</b>			
Bromus carinatus (California brome grass)	2-4	3	39
Hordeum murinum (wall barley)	2-4	7	39
Bromus mollis (soft brome)	3-5	10	37
Lolium multiflorum (Italian ray grass)	3-7	50	36
Lolium perenne (English ray grass)	3-7	7	36
Distichlis stricta (salt grass)	5-7	5	32
Festuca megalura (rattail fescue)	2-5	10	32
<b>Under 31 microns diameter</b>			
Polypogon monspiliensis (beard grass)	3-7	2	30
Cynodon Dactylon (Bermuda grass)	2-11	120	26
Poa annua (annual blue grass)	1-3	3	25



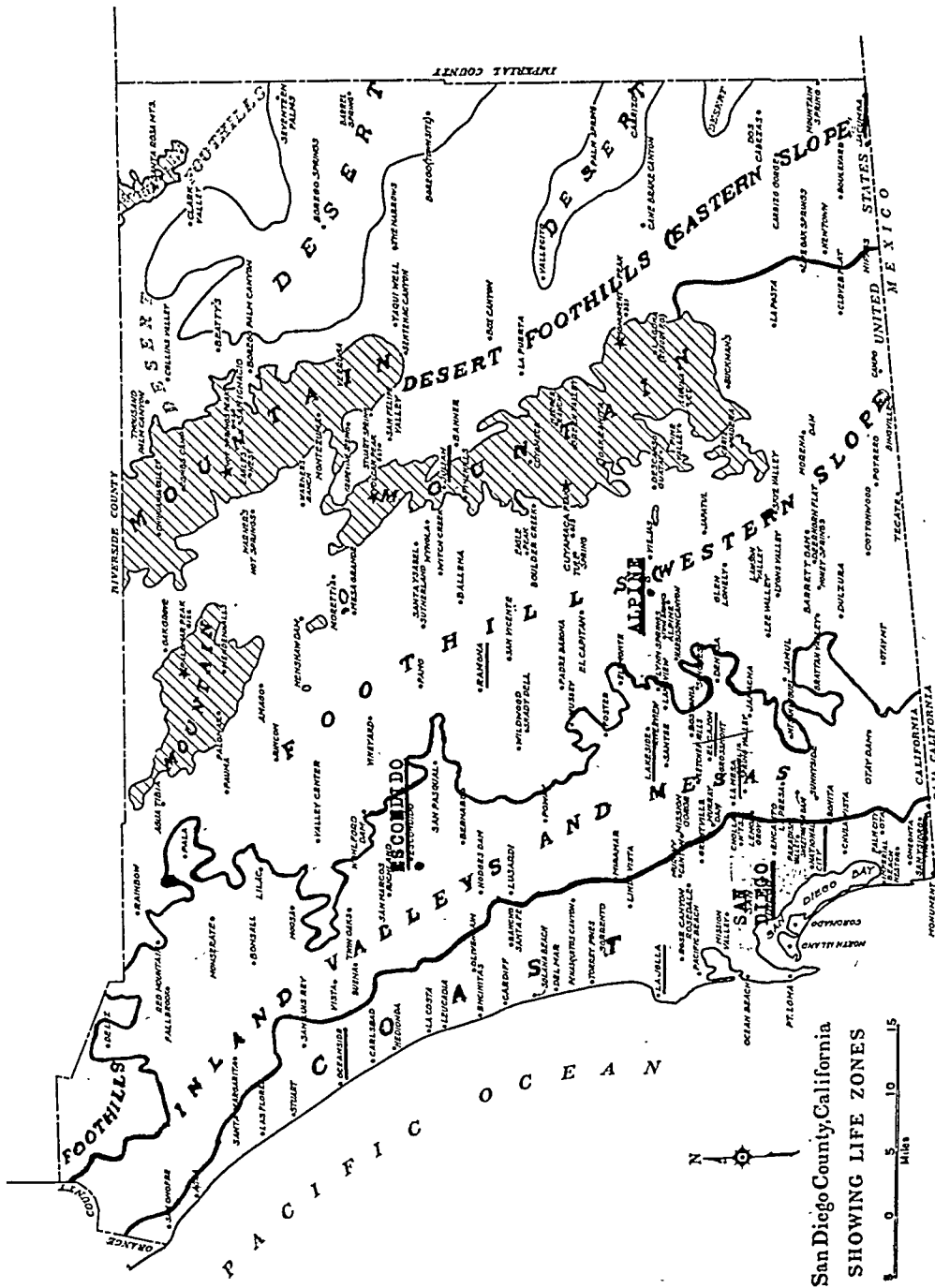


Fig. 1. Map of San Diego County

# POLLINOSIS—HARSH ET AL.

## POLLEN COUNTS OF SAN DIEGO, CALIFORNIA ~1936

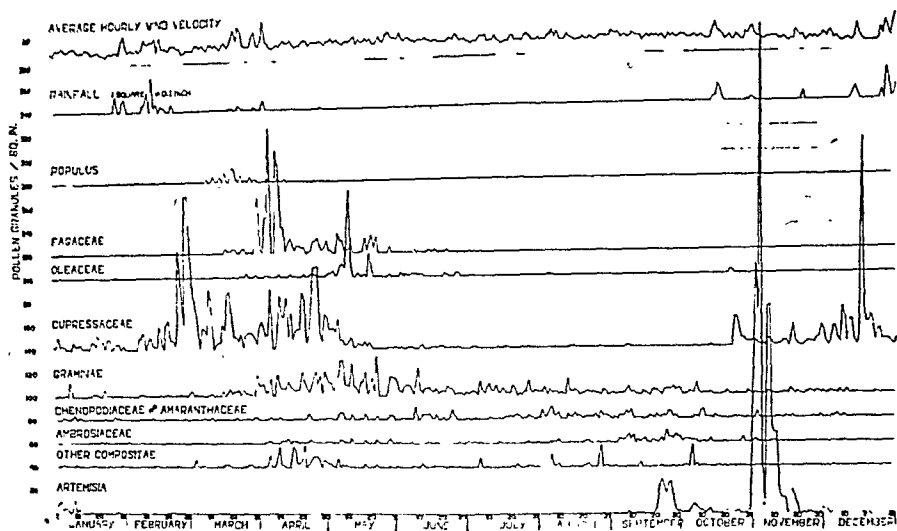


Chart I. Pollen Count for San Diego, California, 1936

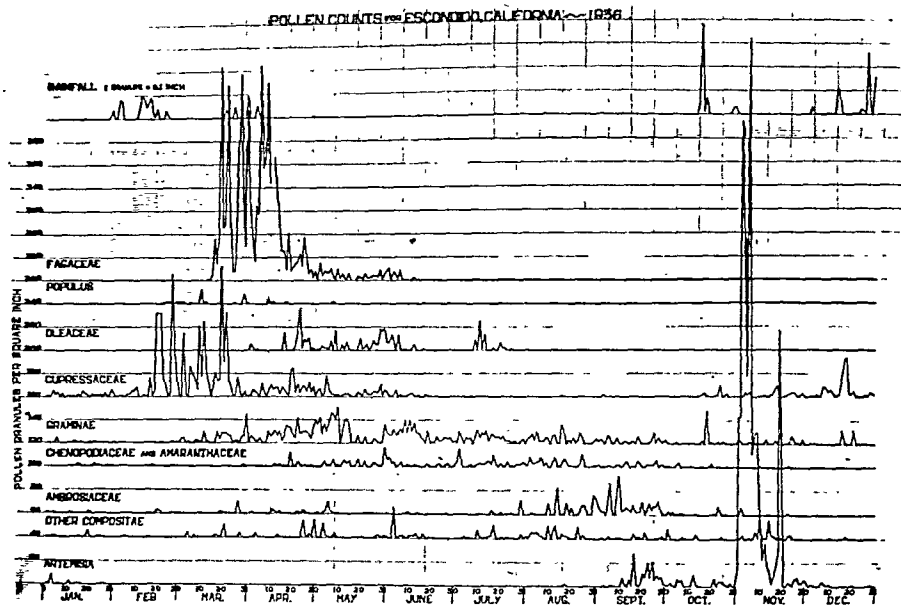


Chart II. Pollen Count for Escondido, California, 1936

It will be seen that the factors in the accompanying formula correspond to three of the five postulates enumerated by Thommen<sup>2</sup> which determine the importance of a given species in pollinosis. A fourth factor, toxicity, is left out of the equation inasmuch as it varies with each patient. The fifth factor, namely, that the species be wind pollinated, is not absolutely essential.

Data collected over a period of seven years in the study of the etiology

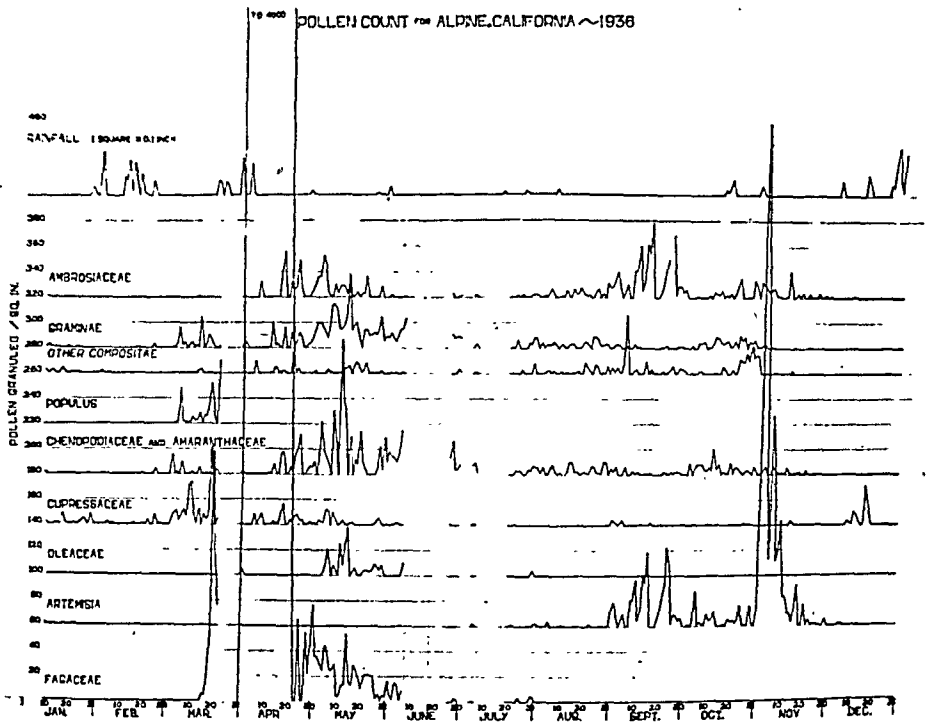


Chart III. Pollen Count for Alpine, California, 1936

of pollinosis in San Diego County, were subjected to evaluation by means of this formula.

#### PROCEDURE

San Diego County is approximately the size of the state of Connecticut. It is bounded on the west by the Pacific Ocean and on the east by the Colorado Desert. Its northern and southern boundaries pass through thinly populated areas. The Coast Range runs north and south through the center of the county and rises to as high as 6,500 feet. The prevailing winds are westerly so that in consequence the relative humidity is quite high along the coast and very low along the eastern border. Rainfall averages about ten inches at the coast, as high as 30 inches in the mountains, and about 2.5 inches at the eastern border. The rains occur almost exclusively in the winter months. Killing frosts are unknown in the coastal area but may occur in the mountains. The map indicates that the topography of San Diego County falls into six fairly distinct life zones, namely, the coast, the inland valleys and mesas, the western foothills of the Coast Range, the mountains, the eastern foothills, and the desert. The last three are sparsely populated.

In 1936, Stealy and McMichael<sup>12</sup> published the results of daily pollen counts at four representative stations within the city limits of San Diego. In this present study the observations at the central station in San Diego were continued as representative of the coastal life zone and in addition, observations were made at Escondido as representative of the inland valleys and mesas and at a resort thirty miles inland, at an elevation of 2,200

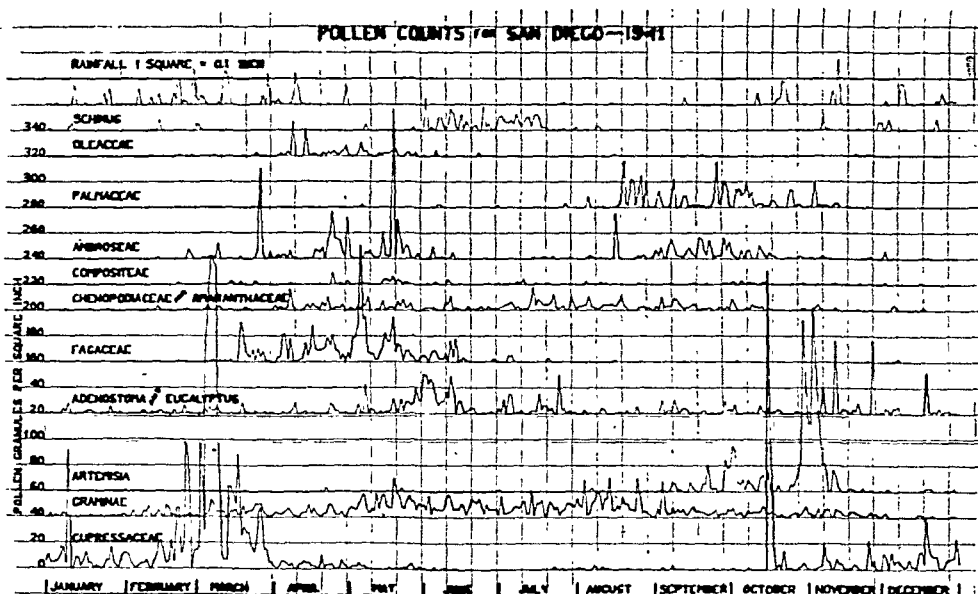


Chart IV. Pollen Count for San Diego, California, 1941

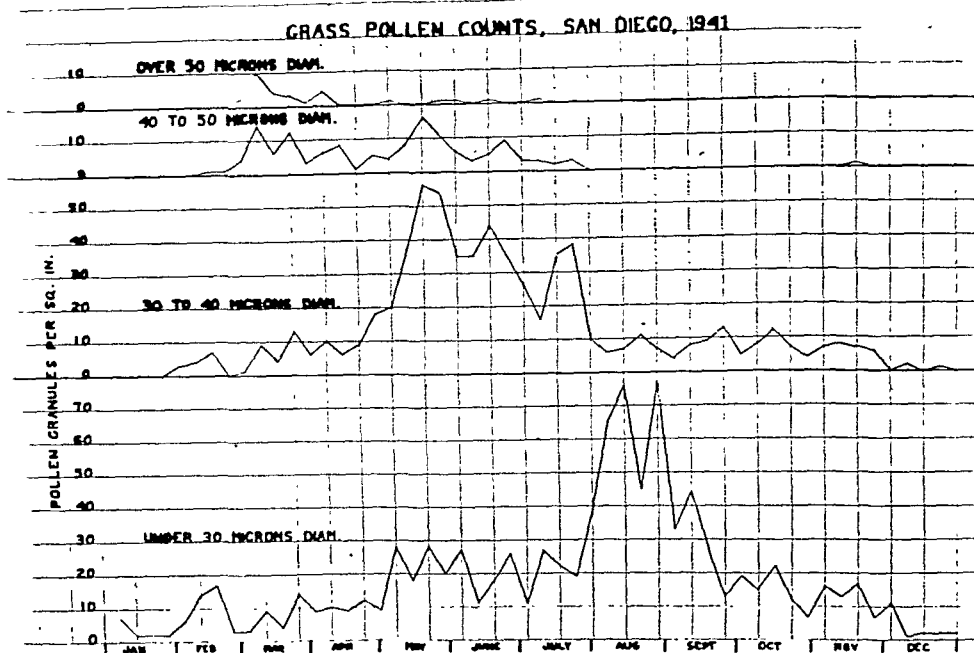


Chart V. Grass Pollen Counts, San Diego, California, 1941

feet, located two miles east of the village of Alpine, as typical of the western foothills region. Charts I, II, and III give the results of these pollen counts for the more important groups of pollens and Table I gives the sum of the daily pollen counts for one year of each pollen group identified. The values in the charts represent the pollen found on one square inch of slide after a twenty-four-hour exposure. The slides were exposed horizontally in a sheltered holder at the level of the roof of a two-story

TABLE III. HAY FEVER PLANTS OF SAN DIEGO COUNTY, CALIFORNIA  
Relative Abundance—Scale 1-10

	Oceanside	La Jolla	W. San Diego	E. San Diego	Coronado	National City	San Ysidro	COAST	La Mesa	El Cajon	Lakeside	Escondido	Fallbrook	VALLEYS	Ramona	Alpine	Julian	Jacumba	MOUNTAINS	SAN DIEGO COUNTY
POLYGONACEAE (buckwheat family)																				
Rumex crispus (curly dock)	1	2	1—	1	1—	2	1	1	2	2	3	3	2	2	2	1	2	1	1	2
CHENOPODIACEAE (goosefoot family)																				
Chenopodium murale (nettle-leaf goosefoot)	3	2	2	2	3	5	3	3	3	1	1	1	2	3	1	1	1	1	1	3
Chenopodium album (lamb's quarters)	1	1	1—	3	1	1	1	2	1—	3	4	3	5	3	1	1	1	1	1	3
Chenopodium ambrosioides (Mexican tea)																				1
Atriplex semilacata (Australian saltbush)	4	8	6	5	8	1	1	7	4	2	5	1—	1	1—	4	4	2	2	3	1
Atriplex Breweri (fencible)	2	3	1	1—	1	—	5	1	1			3		1		1	5	5	1	1
Atriplex canescens (shad scale)																				1
Salicornia pacifica (pickleweed)	6	2	5	1	6	6	1—	4	1					1—						3
Suaeda californica (sea blite)		2	2	1—	5	4	4	3	1—	1	3			1	1—	2				2
Salsola kali, tenuifolia (Russian thistle)	1	2	2	2	1	1	3	2	2											3
AMARANTHACEAE (amaranth family)																				
Amaranthus retroflexus (rough pigweed)			1—	1		4	2	2	2	1	1	6	4	3	1				1—	2
PLATANACEAE (sycamore family)																				
Platanus racemosa (western sycamore)		1—	1—	1		1—	1—	1—	1—		1	1—	2	1	1—	2			1—	1
LEGUMINOSAE (pea family)																				
Acacia (sps) (acacia)	3	3	2	4	2	3	1—	3	4	3	1	2		2	2		1	1	1	2
ANACARDIACEAE (sumac family)																				
Schinus molle (pepper tree)	1	1	4	4	3	5	1	4	3	3	6	2	1	4	1			1—		3
MYRTACEAE (myrtle family)																				
Eucalyptus (sps)	5	3	2	4	3	4	2	4	5	5	6	5	2	5	1	1		1—		4
OLEACEAE (olive family)																				
Olea europea (olive tree)	2	1—	1	1		4	1—	2	3	5	4	1	6	4		1		1—		3
COMPOSITAE (composite family)																				
Hymenoclea monogyra (desert fragrance)																				
Ambrosia psilostachya (western ragweed)	4	3	3	5	1—	2	2	4	7	7	8	8	7	2	6	5	5	4	5	2
Franseria bipinnatifida (false ragweed)																				6
Xanthium bipinnatifida (beach bur)	6	4	4	1	7	5	1	1—			1—			1—				3	1	1
Xanthium pennsylvanicum (cocklebur)	1—	1	1	3	1—	2	1	2	1	1	2	5	1	3	2	1	2	1—	2	3
Artemisia californica (coast sagebrush)	4	10	7	6	1—	6	3	7	8	6	8	9	8	9	8	6	3	1—	2	1—
Artemisia dracunculoides (Indian hair tonic)		1	1—	2	1	1—	1	1—	1		1—		1—	1—	1—	2	1	1	1	1
Artemisia Douglasi (mugwort)						1—						3	1—	1—						1

TABLE III. HAY FEVER PLANTS OF SAN DIEGO COUNTY, CALIFORNIA  
Relative Abundance—Scale 1-10

	Oceanside	La Jolla	W. San Diego	E. San Diego	Coronado	National City	San Ysidro	COAST	La Mesa	El Cajon	Lakeside	Escondido	Fallbrook	VALLEYS	Ramona	Alpine	Julian	Jacumba	MOUNTAINS	SAN DIEGO COUNTY
PINACEAE (pine family)																				
Cupressus macrocarpa (Monterey cypress)	5	2	3	4	3	2		4				2	1	1			1-			3
Juniperus californica (Calif. juniper)																				1
GRAMINEAE (grass family)																				
Sorghum halepense (Johnson grass)	1	3		1	1	1	1	1	1	1	3	5	3	2	2				1	2
Echinochloa crus-galli (barnyard grass)																				1
Phalaris minor (small canary grass)	2	1	1	1	1	1	1	1	1	1	5	4	7	3	6	1	1-		1	1
Polypogon monspeliensis (beard grass)	9	7	8	8	3	8	6	8	10	10	5	10	7	8	6	5	3	1-	6	4
Avena fatua (common wild oats)	6	10	5	3	8	3	5	6	6	6	5	10	3	7	5	3	3		4	7
Avena barbata (slender wild oats)	4	6	8	7	8	8	5	7	6	4	5	10	3	4	5	4	3		4	4
Cynodon Dactylon (Bermuda grass)																				
Spartina tectanthe (cord grass)	3	4	6	1	5	3	2	4	3	2	2	2	1	2	1		2		1	2
Distichlis stricta, laxa (salt grass)																				
Poa annua (annual blue grass)	6	5	5	5	5	5	5	6	3	3	4	8	10	8	4	6	1-		1	1
Festuca megastura (rattail fescue)	3	1	1	2	1	2	1	3	2	2	1	1	1	1	1	1	5		5	1
Bromus carinatus (Calif. brome grass)	3	1	1	2	1	3	1	3	2	1	1	5	6	7	8	6	1		1	1
Bromus mollis (soft brome grass)	6	4	6	4	3	4	4	5	10	5	6	5	6	4	5	6	5		6	6
Bromus rubens (red brome grass)	3	3	4	5	4	5	4	4	4	5	4	2	3	7	3	3	2		4	4
Bromus rigidus (broncho grass)	6	8	5	5	5	4	6	6	2	2	6	6	1	6	4	6	6		5	6
Lolium multiflorum (Italian ray grass)	6	4	2	5	1	6	4	5	5	4	1	6	1	4	4	3	3		2	4
Lolium perenne (English ray grass)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	5	3		1	1
Lolium multiflorum (Italian ray grass)	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	3		1	1
Hordeum murinum (wall barley)	6	8	7	7	5	7	6	6	6	4	5	6	6	5	5	5	6		4	5
SALICACEAE (willow family)																				
Populus Fremontii (Fremont cottonwood)	3	1	1	3	1	1	4	2	1	5	2	1	3	3	3	3	4		2	3
Salix lasiolepis (arroyo willow)																	1		2	
BETULACEAE (birch family)																				
Alnus rhombifolia (white alder)								1-								1	1		1	1-
FAGACEAE (beech family)																				
Quercus Kelloggii (Calif. black oak)																				
Quercus agrifolia (coast live oak)																				
Quercus Engelmannii (mesa oak)																				
Quercus dumosa (scrub oak)																				
Quercus chrysolepis (maul oak)																				
URTICACEAE (nettle family)																				
Urtica gracilis, holoserica (creck nettle)			1-					1-			1-	1-	3-	1		1	2		1	1

TABLE IV. PERTINENT DATA ON PLANTS OF IMPORTANCE IN POLLINOSIS IN SAN DIEGO COUNTY, CALIFORNIA

	Pollinating period (in months of year)	Pollen size (in microns)	Pollen production at maximum intensity*	Percentage of patients reacting			Plant abundance (Scale 1-10)	Importance (disregarding toxicity)†
				1 +	2-4 +	Total		
PINACEAE (pine family)								
Cupressus macrocarpa (Monterey cypress)	12- 5	25	400	10	3	13	3	300
Juniperus californica (California juniper)	11- 5	32	200	2	1	3	1	40
GRAMINEAE (grass family)								
Sorghum halepense (Johnson grass)	5- 9	43	20	20	12	32	2	7
Echinochloa crus-galli (barnyard grass)	7-10	33	7			20	1	2
Phalaris minor (small canary grass)	4- 6	39	35	18	16	34	1-	1
Polypogon monspiliensis (beard grass)	3- 7	30	7				2	2
Avena fatua (common wild oats)	2- 4	53	25	11	15	26	7	10
Avena barbata (slender wild oats)	2- 4	43	4	12	17	29	5	1
Cynodon Dactylon (Bermuda grass)	2-11	26	45	22	24	46	7	120
Spartina leiantha (cord grass)	6- 9	47	10	11	24	35	2	4
Distichlis stricta, laxa (salt grass)	5- 7	32	20	24	16	40	2	5
Poa annua (annual blue grass)	1- 8	25	+	15	18	33	1	3
Festuca megalura (rattail fescue)	2- 5	32	10	14	19	33	8	10
Bromus carinatus (Calif. brome grass)	2- 4	39	12	13	15	26	2	3
Bromus mollis (soft brome grass)	3- 5	37	19	17	15	32	6	10
Bromus rigidus (broncho grass)	4- 5	43	70	15	13	28	6	20
Lolium multiflorum (Italian ray grass)	3- 7	36	105	22	23	45	4	50
Lolium perenne (English ray grass)	3- 7	36	95	22	20	42	1-	7
Hordeum murinum (wall barley)	2- 4	39	17	21	12	33	5	7
PALMACEAE (palm family)								
Cocos plumosa (plumosa palm)	8-11	35				6	3	10
SALICACEAE (willow family)								
Populus Fremontii (Fremont cottonwood)	3	30	170	8	11	19	2	7
Salix lasiolepis (arroyo willow)	2- 5	18	5			10	3	5
JUGLANDACEAE (walnut family)								
Juglans regia (English walnut)	4- 5	45	350	7	1	8	1-	4
BETULACEAE (birch family)								
Alnus rhombifolia	1- 2	24	300	1	1	2	1-	5
FAGACEAE (beech family)								
Quercus agrifolia (coast live oak)	3- 5	30	350	13	5	18	8	300
Quercus Engelmannii (mesa oak)	4- 5	28		15	7	22	3	70
Quercus dumosa (scrub oak)	4- 5	30	300	12	10	22	3	80
Quercus chrysolepis (maul oak)	5- 6	28					2	50
URTICACEAE (nettle family)								
Urtica gracilis, holoserica (creek nettle)	6- 8	15	9	11	3	14	1	4

\*Franseria acanthicarpa = 100. See p. 28.

†See p. 28 for formula used in calculating importance.

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TABLE IV. PERTINENT DATA ON PLANTS OF IMPORTANCE IN POLLINOSIS IN SAN DIEGO COUNTY, CALIFORNIA

	Pollinating period (in months of year)	Pollen size (in microns)	Pollen produc- tion at maximum intensity*	Percentage of patients reacting			Plant abund- ance (Scale 1-10)	Import- ance (disre- garding toxicity**
				1 +	2-4 +	Total		
<b>POLYGONACEAE</b> (buckwheat family)								
<i>Rumex crispus</i> (curly dock)	2- 4	25	21			18	2	5
<b>CHENOPODIACEAE</b> (goosefoot family)								
<i>Chenopodium murale</i> (nettle-leaf goosefoot)	3- 7	21	13	12	8	20	3	20
<i>Chenopodium album</i> (lamb's quarters)	4- 9	25	55	12	10	22	2	25
<i>Chenopodium ambrosioides</i> (Mexican tea)	7-11	21	+			21	1	2
<i>Atriplex semibaccata</i> (Australian saltbush)	5-10	18	+ -				5	3
<i>Atriplex Breweri</i> (lenscale)	8-10	19	75	13	7	20	1 -	7
<i>Atriplex canescens</i> (shad scale)	6- 8	25	60	14	3	17	1	8
<i>Salicornia pacifica</i> (pickleweed)	6-10	23	20	17	8	25	2	12
<i>Suaeda californica</i> (sea blite)	7-11	25	20	11	3	14	2	8
<i>Salsola kali, tenuifolia</i> (Russian thistle)	6-10	25	30	14	12	26	2	15
<b>AMARANTHACEAE</b> (amaranth family)								
<i>Amaranthus retroflexus</i> (rough pigweed)	6- 9	28	5	15	7	22	2	2
<b>PLATANACEAE</b> (sycamore family)								
<i>Platanus racemosa</i> (western sycamore)	3- 4	18	++	11	8	19	1	2
<b>ROSACEAE</b> (rose family)								
<i>Adenostoma fasciculatum</i> (chamise)	4- 7	17	20	13	7	20	6	30
<b>LEGUMINOSAE</b> (pea family)								
<i>Acacia</i> sps. (acacia)	1- 5	43		5	0	5	2	3
<b>ANACARDIACEAE</b> (sumac family)								
<i>Schinus molle</i> (pepper tree)	4-10	25	8	21	5	26	4	15
<b>MYRTACEAE</b> (myrtle family)								
<i>Eucalyptus</i> sps.	1- 8	25	1	11	4	15	4	2
<b>OLEACEAE</b> (olive family)								
<i>Olea europea</i> (olive tree)	4- 6	22	42	10	7	17	3	25
<b>COMPOSITAE</b> (composite family)								
<i>Hymenoclea monogyra</i> (desert fragrance)	10	21	135	17	11	28	2	15
<i>Ambrosia psilostachya</i> (western ragweed)	7-10	25	50	15	19	34	6	60
<i>Franseria acanthicarpa</i> (false ragweed)	7- 9	21	100	15	21	36	1 -	7
<i>Franseria bipinnatifida</i> (beach bur)	2-11	25	17	16	17	33	3	25
<i>Xanthium pennsylvanicum</i> (cocklebur)	7- 9	25	25	19	17	36	2	7
<i>Artemisia tridentata, angustifolia</i> (sagebrush)	10	25	150	20	18	38	3	20
<i>Artemisia californica</i> (coast sagebrush)	10-11	21	40	14	34	48	16	90
<i>Artemisia dracunculoides</i> (Indian hair tonic)	7- 9	21	++	16	31	47	1	4
<i>Artemisia Douglasiana</i> (mugwort)	8-10	25	70	16	31	47	2	20



building. In Chart IV the pollen counts at the San Diego station for 1941 are given for comparison. Further explanation of Charts I to IV will be found under the section on "Interpretation of Charts."

The pollen included under the *Gramineae* (grass family) represent a particularly large number of species. In order to obtain some idea as to the grasses with which we were dealing and incidentally to add to our knowledge of the effect of the size of the grains on the ability of pollen to travel in the air, we measured every grass pollen grain found on our slides throughout the year 1941. Grass pollen counts, divided according to size, are shown graphically in Chart V. The sum of the daily grass pollen counts of each size group for the year 1941, is appended to Table I. Table II indicates the grass pollen grain which would fall within the arbitrarily selected size groups. It should be realized that the figures for pollen size represent averages, and that the actual diameter may vary as much as 5 microns either way from the figures given for the smaller sizes and as much as 10 microns for the larger sizes. Also there is a certain amount of overlapping in contiguous groups. This is indicated approximately by the brackets to the right in Table II.

In Table III, the relative abundance, on a scale of 1 to 10, of each species of the plants of possible importance in pollinosis is recorded for each community in this county having a population of 1,000 or over. These values were determined by a careful survey of each locality at least every two or three months, over a period of four years. More frequent visits were often necessary in order to study some particular species. In addition, similar notes were made for the territories between centers of habitation. Both sets of data were considered in determining the values for each life zone and for the county as a whole. A "1-" indicates that the plant was present but not in sufficient abundance to be of any importance.

Table IV summarizes all of the remaining data necessary to determine the importance of each plant. The pollinating dates given are the results of direct field observations. They were compared with data given by Hall<sup>5</sup>, Piness, Miller and McMinn<sup>10</sup>, Rowe<sup>11</sup>, and McMinn.<sup>8</sup> Whenever marked differences occurred, the dates were carefully checked in succeeding years. It should be realized, however, that the pollination period for certain species may vary markedly from year to year depending chiefly on the occurrence of rains. Thus *Artemisia californica* (coast sagebrush), which usually pollinates in November, may do so as early as September or as late as January. Certain other dates are remarkably constant. For example, the onset of the pollinating season of *Hymenoclea monogyra* (desert fragrance) will rarely vary more than one or two days from the first day of October.

The pollen grain sizes were determined by actual measurement, the figures given representing average sizes. As already stated, the sizes of individual pollen grains of the same species may vary considerably. The fig-

ures compare fairly well with the measurements of Duke<sup>4</sup>, Wodehouse<sup>13</sup>, and Piness and McMinn.<sup>9</sup>

The amount of pollen produced by each plant was estimated in the following manner. The flowering heads from one square meter, or definite fraction or multiple thereof, of a pure stand of the species in question, were gathered as nearly as possible at the peak of pollination. The stems were placed in water in a quiet, sunny room, and glazed paper was spread beneath the flowers. After forty-eight hours the heads were shaken and the amount of pollen collected and weighed. At least two, and usually three, separate collections were made and weighed separately for each species.

The percentage of pollen-sensitive patients reacting to each species was determined by routine scratch tests. This total was subdivided into those slightly but definitely sensitive (one plus) and those strongly sensitive (two to four plus). Only one species (*Acacia*) failed to produce any strong reactions.

The figures for plant abundance are taken from the final column of Table III. These figures represent an estimate for the county as a whole, and hence may be different from the figures for any specific locality or life zone as given in Table III.

The figures designating the importance of each plant were determined by calculation, using the formula already stated. The results of the calculations are given in round numbers so as not to give a false impression of accuracy. In a few instances the calculated result was modified if it seemed to conflict with known data from direct pollen counts, due regard to the volume of the pollen grains being given. In certain instances the value taken for "n" (the number of months of pollination) was less than the time indicated in the first column since the bulk of pollination for certain plants occurs during a relatively short time, sometimes only a few days, although the plant may pollinate lightly over a long period.

#### INTERPRETATION OF CHARTS

Field studies of pollinating dates, distribution of plants, and amount of pollen produced, together with a knowledge of the topography of the area and of the prevailing direction of the wind, enable us to interpret the various graphs in Charts I to IV with a fair degree of accuracy. The following remarks regarding the composition of the different groups should help to clarify the meaning of the charts.

*Charts I, II and III.*—*Populus* pollen comes from *Populus Fremontii* (Fremont cottonwood).

*Fagaceae* pollen comes chiefly from *Quercus agrifolia* (coast live oak) and *Quercus dumosa* (scrub oak) in San Diego, *Quercus agrifolia* in Escondido, and that species plus *Quercus Engelmannii* (mesa oak) at Alpine.

*Oleaceae* pollen is due entirely to olive trees since *Ligustrum* (privet)

which is of the same family can be differentiated microscopically and was counted separately.

*Cupressineae* comes from *Cupressus macrocarpa* (Monterey cypress) with perhaps a little *Juniperus californica* (juniper) pollen when the wind comes from the east.

*Gramineae*. The composition of this group should be apparent from a study of Chart V and Table II.

*Chenopodiaceae* and *Amaranthaceae* comprise a large group. However, studies of the importance of the various species (Tables III and IV) indicate that *Chenopodium murale* (sowbane) and *Chenopodium album* (lamb's quarters) make up the larger part of this group in the spring, with perhaps some help from *Atriplex semibaccata* (Australian saltbush); the remaining members of these two families account for the late summer and fall pollens of this group.

*Ambrosiae* must be due entirely to *Franseria bipinnatifida* (beach bur) in the spring, with the remainder of the group, chiefly *Ambrosia psilostachya* (western ragweed) contributing the fall contingent.

*Artemisia*. The early rise is accounted for by *Artemisia Douglasiana* (mugwort) with lesser help from *Artemisia dracunculoides* (dragon sage); *Artemisia californica* (coast sagebrush) accounts for the marked rise which occurs later.

Chart IV. *Schinus* comes entirely from *Schinus molle* (pepper tree).

*Palmaceae* is due chiefly to *Cocos plumosa* (plumosa palm).

*Adenostoma* and *Eucalyptus* are not related botanically although their pollen grains are identical morphologically except for size. It was realized too late in our study that these two could be differentiated fairly well by size alone and could have been plotted separately. However, most of the pollen represented by this curve in May, June, and July, comes from *Adenostoma fasciculatum* (chamise).

Chart V.—The meaning of Chart V should be apparent from Table II and the latter part of Table I.

Grass pollen grains under 31 microns in diameter come essentially from Bermuda grass. It is interesting to note that the peak comes in August and September rather than in the spring.

The group of grains from 31 to 40 microns in diameter is composed approximately of two parts *Lolium* pollen (ray grass, chiefly Italian ray grass), and one part that of other members of this group.

The group of grains 41 to 50 microns in diameter is dominated by those of *Bromus rigidus* (broncho grass).

The group of grains *over 50 microns* in diameter is made up chiefly of *Avena fatua* (common wild oats) plus some *Spartina leiantha* (cord grass). It should be remembered that although the total number of pollen grains of the large sizes is small the amount of allergen present in each is, in all probability, proportionate to the mass of the granules. The volume of a grain of common wild oat pollen, for example, is ten times that of one of Bermuda grass pollen, that of Broncho grass is five times greater, and that of Italian ray grass, three times greater. Moreover, the number of pollen grains of the larger sizes present in the air is undoubtedly much greater at ground level than at the level of the roof of a two-story building where our slides were exposed.

#### DISCUSSION

*Theory.*—To adherents of the theory that testing and treating for the pollen of one species of a family is sufficient for all members of that family, this whole study will seem like "Much ado about nothing." It is not the purpose of this study to deal with that theory. However, one fact in our experience would seem to be an insurmountable obstacle to its acceptance. Many patients will react strongly to the pollen of *Cynodon Dactylon*, *Distichlis stricta* and *Spartina leiantha*, which are closely related grasses, and fail to react to that of all other grasses, whereas the reactions of certain other patients will be just the reverse.

*Factual Data.*—From Charts I, II, and III, it will be seen that on the whole, the amount of pollen is greater in Escondido than in San Diego and greater in Alpine than in Escondido. This is to be expected since the prevailing winds are westerly. The enormous values for oak pollen at Alpine may be somewhat deceptive, since, in spite of these high values, and in spite of moderately frequent skin reactions to oak pollen, proven cases of clinical sensitivity to this allergen are not common. Likewise, only a few cases of clinical sensitivity to cypress pollen have been found. The incidence of *Chenopodiaceae* pollen at Alpine in April, May, and June is high but since this pollen can come only from sowbane, lamb's quarters, and possibly some from Australian saltbush, which are not common in that locality, the pollen must be carried in by the wind. The rise in ambrosia-like pollen at Alpine during April and May is even more striking since this could come only from *Franseria bipinnatifida* or beachbur which grows only on a narrow strip of beach along the entire coast of California. Study of a relief map revealed the fact that a river valley extends from an area of the beach, where this species grows in great abundance, to Alpine and allows a clear sweep for a southwest wind to carry this pollen inland. No similar rise in this pollen curve occurs at Escondido because that city is protected from the beach by a range of hills to the west.

A study of Table III indicates that each locality presents a problem in itself. It is regrettable that data on many other communities had to be

omitted due to limitations of space. The western border of Balboa Park was taken arbitrarily as the dividing line between West San Diego and East San Diego. West San Diego includes Mission Beach, Ocean Beach and Point Loma. Coronado includes North Island and the strand which connects Coronado with the mainland. The area designated "mountains" actually includes the western and eastern foothills life zones as well. The coastal life zone might well be subdivided into the immediate coast comprising the beaches and salt marshes, and the area farther inland. Each has a characteristic flora and the treatment for a housewife living near the beach, for example, should be different from that for one living in East San Diego.

An example as to how the information contained in this study is utilized may be of interest. After determining a patient's pollen sensitivities by skin tests, we note the importance of the reacting species for the county as a whole from Table IV. We then consider from Table III the abundance of these plants in the life zone and also in the community in which the patient lives. In some cases it may be advisable to visit his home also, since species of no general importance may be quite important if they occur near the patient's residence, especially if outside his bedroom window. The ratio of the various pollens to be included in the treatment mixture is determined by the probable ratio of each in the atmosphere to which he is exposed, due regard being given to the degree of his sensitivity to each species.

Additional facts of interest concerning each plant species, which could not be presented in tabular form, are given in the supplement.

#### SUMMARY

1. A mathematical formula for determining the importance of a given plant species in pollinosis in any locality is proposed.
2. Charts of daily pollen counts for one year at three representative localities in San Diego County are presented.
3. The size of each grass pollen grain found on our slides during one year was measured and charted.
4. A botanical survey of plants of importance in pollinosis in this county is given.
5. The percentage of patients reacting to each species is given.
6. Data on the pollinating period, the amount of pollen produced, the size of the pollen grains, and the abundance of each species are given, evaluated by means of the formula, and correlated with the data referred to in points 2 through 4 of this summary.

We wish to acknowledge with sincere appreciation, the help of Dr. C. A. S. Kemper of Escondido and Misses Betty and Susan Noble of Alpine in exposing the slides, and of Mr. Frank Gander, head of the Botany Department of the San Diego Museum of Natural History, in identifying plant specimens.

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## SUPPLEMENTARY DATA ON PLANTS OF REAL OR SUPPOSED IMPORTANCE IN POLLINOSIS, IN SAN DIEGO COUNTY, CALIFORNIA\*

### SPERMATOPHYTES (seed-producing plants, flowering plants)

#### GYMNOSPERMAE (conifers, cone-bearing plants, naked-seed plants, evergreens)

##### *Pinaceae* (pine family)

##### *Pinus*, sps. (pine tree)

Toxicity questionable. However, Rowe has reported a proven case of severe allergy to tamarack pine.

##### *Cupressus macrocarpa* (Lambertiana m.) (Monterey cypress)

A heavy producer of pollen but the toxicity is low. Nevertheless a few cases of proven allergy to this pollen have been found.

##### *Juniperus californica* (California juniper, "cedar"†)

Same comment applies as for the preceding species. In addition this species grows in the most thinly populated section of the county, namely the arid eastern slope of the Coast Range.

#### ANGIOSPERMAE (plants with enclosed seeds)

#### MONOCOTYLEDONES (one rudimentary leaf in the embryo, leaves usually parallel-veined)

##### *Gramineae* (Poaceae) (grass family)

##### *Andropogoneae* (beard grass tribe)

##### *Andropogon saccharoides* (beard grass)

Unimportant.

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\*All wind-pollinated species are considered of some importance unless otherwise indicated.

†Quotation marks enclosing common names indicate that the names are incorrectly applied.

*Sorghum halepense* (*Andropogon* h., *Holcus* h.) (Johnson grass, evergreen millet, Egyptian millet, St. Mary's grass, Cuba grass, Means grass, Aleppo grass, Syrian grass)

Roadsides and ditches.

Panicaceae (panic grass tribe)

*Digitaria sanguinalis* (*Panicum sanguinale*, *Syntherisma sanguinale*)  
(crab grass, "Devil grass")

Orchards and citrus groves. Said to be largely close-pollinated, hence probably of no importance. (Some botanists believe all grasses are self-pollinated to some extent).

*Echinochloa crus-galli* (*Panicum* c.-g., *Oplismenus* c.-g.) (barnyard grass, barnyard millet)

A weed in cultivated fields, groves, and orchards.

*Setaria lutescens* (bristly foxtail)

Unimportant.

Phalarideae (canary grass tribe)

*Phalaris minor* (small canary grass, Mediterranean canary grass)

Much less abundant now than formerly.

*Phalaris canariensis* (canary grass, bird-seed grass)

Unimportant.

Agrostideae (bent grass tribe)

*Stipa coronata* (giant stipa, giant spear grass)

Dry slopes and mesas. A heavy producer of pollen but distribution is scant.

*Stipa pulchra* (*S. setigera*) (needle grass, nodding stipa)

Of minor importance.

*Stipa lepidota* (*S. eminens*) (small-flowered stipa)

Of minor importance. Note: no one of the genus *Stipa* is important but it is wise to include either the strongest reactor or a mixture of all three in the treatment antigen of patients reacting strongly to this group.

*Polypogon monspiliensis* (beard grass, annual beard grass, tawny beard grass)

In low places. Fairly abundant but pollen production is scant.

*Agrostis alba* (redtop, marsh or creeping bent grass, whitetop)

Large reactions are often obtained with this pollen, especially in patients who have lived in the East or in Hawaii but it is too rare to be of any importance in this county.

Aveneae (oat tribe)

*Koeleria cristata* (Koeler's grass, "June grass")

Rare.

*Avena fatua* (common wild oats)

Much over-rated as a cause of pollinosis. Abundant.

*Avena barbata* (slender wild oats, barbed oats)

A poor producer.

Chlorideae

*Cynodon Dactylon* (*Capriola Dactylon*) (Bermuda grass, "devil grass," scutch grass, wire grass, "salt grass" chicken foot, Indian couch grass)

Lawns and roadsides everywhere. The most important grass in pollinosis in this county. Said to pollinate chiefly at night. Pollinates all year but more in July and August in this vicinity. Some patients react only to this species, cord grass and salt grass and to no other grasses.

*Spartina leiantha* (*S. foliosa*) (cord grass)

## POLLINOSIS—HARSH ET AL.

Occurs as a pure growth in large salt marshes along the coast. Some pollen of its size was found on our slides during its pollinating season.  
*Chloris virgata* (Rhodes grass)

Unimportant.

### Festuceae (fescue tribe)

*Distichlis stricta, laxa* (*D. spicata*) (salt grass)

Abundant only in salt marshes along the coast. A dioecious grass. Sometimes mistaken for Bermuda grass but the flowering head is entirely different.

*Dactylis glomerata* (orchard grass)

Unimportant although many patients react strongly to it.

*Lamarkia aurea* (*Achyrodes a.*) (golden top, toothbrush grass)

Most of the florets are sterile and hence produce no pollen. Unimportant.

*Poa annua* (annual blue grass, low spear grass, six-weeks grass, dwarf meadow grass)

Lawns. Will flower when only one or two inches high so mowing does not eliminate its pollination.

*Poa pratensis* (June grass, Kentucky blue grass, spear grass, common meadow grass, green grass)

Occurs abundantly in lawns but practically none ever pollinates because it is kept cut, hence is of no importance. It will not grow in this vicinity without artificial watering.

*Festuca megalura* (practically identical with *F. myuros* and *F. bromoides*) (rat-tail fescue)

Hills and mesas throughout the county. The most abundant grass in San Diego County. The pollen production is rather scant however.

*Bromus carinatus* (very similar to *B. marginatus*) (California brome - grass)

Waste places.

*Bromus mollis* (*B. hordeaceus*) (soft brome grass, soft cheat, soft chess, "poverty grass")

Abundant but much of it grows in fields with much taller wild oats and other grasses, so its pollen is not easily caught by the wind.

*Bromus rubens* (red brome, fox-tail brome grass)

A scant pollinator.

*Bromus rigidus* (*B. maximus*, *B. villosus*) (broncho grass, "fox-tail," rip gut)

The most important of this genus. The bromes taken together are fairly important. It is probably best to include a mixture of all four, in the approximate ratio of their importance, in the antigen of patients sensitive to this group.

### Hordeae (barley tribe)

*Lolium multiflorum* (Italian ray grass, Italian rye grass, Australian rye grass, "darnel")

Abundant in all towns. An escape from cultivation. The most important grass, next to Bermuda, in this county. Very toxic. About 6 to 10 times as abundant as the next species. Makes a quick but coarse lawn.

*Lolium perenne* (perennial ray or rye grass, English ray or rye grass, red ray, red darnel, red dare, English blue grass, "darnel")

Very similar to the preceding but much less abundant.

*Lolium temulentum* (darnel)

Even less abundant than *L. perenne*.



## POLLINOSIS—HARSH ET AL.

*Hordeum murinum* (wall barley, "fox tail," farmer's fox tail)

Pollen production fair.

*Elymus triticoides* (*E. orcuttianus*) (alkali rye grass, slender wild rye)

Unimportant.

*Elymus condensatus* (*E. cinereus*) (giant wild rye)

Canyons. Of slight importance.

*Elymus glaucus* (*E. americanus*) (western rye grass, glaucous wild rye)

Unimportant.

### *Palmaeaceae* (palm family)

*Cocos plumosa* (plumosa palm, cocos palm, plume palm)

The most abundant palm. A feather palm. Reactions to its pollen are small and rare.

*Phoenix canariensis* (Canary-island date palm)

The role of this and other species of palm is doubtful.

DICOTYLEDONES (plants with two rudimentary leaves in the embryo, leaves with netlike veins)

### *Salicaceae* (willow family)

*Populus Fremontii* (Fremont cottonwood, common cottonwood, poplar)

Along stream beds. Dioecious. The "cotton" has nothing to do with pollinosis.

*Salix lasiolepis* (arroyo willow)

Along stream beds. Dioecious. The willow pollens represent a transition stage between insect and wind pollination. The pollen is rather sticky. Several other species of willow occur but this one far exceeds all others combined.

### *Juglandaceae* (walnut family)

*Juglans regia* (English walnut, Persian walnut)

Rare in this county. In regions where it is grown, sensitivity is sometimes severe.

*Juglans californica* (California black walnut)

Too rare to be important.

### *Betulaceae* (birch family)

*Alnus rhombifolia* (white alder)

Only along permanent stream beds.

### *Fagaceae* (beech family)

*Quercus Kelloggii* (California black oak)

A deciduous oak. Occurs at 4,000 to 6,000 feet elevation.

*Quercus agrifolia* (coast live oak, California live oak)

Throughout the county. Marked clinical sensitivity to oak pollen is rare.

*Quercus Engelmannii* (*Q. MacDonaldii*) (Engelman oak, mesa oak, "black oak")

Occurs at 1,800 to 4,000 feet elevation.

*Quercus dumosa* (scrub oak)

Common chaparral shrub.

*Quercus chrysolepis* (maul oak, canyon oak, gold cup oak)

Common in canyons in the higher eastern slopes of the mountains.

### *Urticaceae* (nettle family)

*Urtica gracilis*, *holoserica* (creek nettle)

Along stream banks.

### *Polygonaceae* (buckwheat family)

*Rumex crispus* (curly dock, yellow dock)

Low places. It is surprising that so little dock pollen was found on the slides since it is a good producer and the pollen is light.

## POLLINOSIS—HARSH ET AL.

*Rumex conglomeratus* (green dock)

Unimportant.

*Rumex Acetosella* (sheep sorrel, sour dock)

Rare.

*Chenopodiaceae* (goosefoot, chenopod, pigweed, or saltbush family)

*Chenopodium murale* (nettle-leaf goosefoot, sowbane)

Road sides, orchards and waste places.

*Chenopodium album* (lamb's quarters, white pigweed, white goosefoot)

Common weed.

*Chenopodium ambrosioides* (Mexican tea)

Occasional weed.

*Atriplex rosea* (red scale, red orache)

Unimportant.

*Atriplex semibaccata* (Australian saltbush)

Pollen production scant but pollinating period is prolonged and the plant abundant.

*Atriplex serenana* (*A. bracteosa*) (bract scale)

Unimportant.

*Atriplex Breweri* (Brewer lenscale)

Along the coast especially at La Jolla. Sometimes used as a hedge. Dioecious.

*Atriplex canescens* (*A. tetraptera*) (shad scale, wing scale, four-wing saltbush)

At Sunset Cliffs, Encinitas, San Ysidro and Jacumba. Dioecious.

*Salicornia pacifica* (*S. ambigua*) (pickleweed, samphire, glasswort)

Large areas in salt marshes along the coast.

*Suaeda californica* (*Dondia c.*) (sea blite)

Salt marshes along the coast.

*Salsola kali, tenifolia* (*S. pestifer*) (Russian thistle, "tumbleweed," saltwort)

The most toxic member of this family. A tumbleweed.

*Amaranthaceae* (amaranth or pigweed family)

*Amaranthus retroflexus*, (rough pigweed, redroot pigweed)

Common weed in gardens and orchards.

*Amaranthus graecizans* (tumbling pigweed, tumble-weed)

Also a tumble weed. Pollen production so scant as to make its role doubtful.

*Cruciferae* (mustard family)

*Brassica campestris* (mustard)

Insect pollinated. Conspicuous but probably unimportant.

*Platanaceae* (sycamore family, buttonwood, plane tree family)

*Platanus racemosa* (western sycamore, California plane tree)

Common along stream beds.

*Platanus acerifolia* ("Oriental plane tree," London plane tree, cultivated sycamore)

Grown for shade.

*Rosaceae* (rose family)

*Adenostoma fasciculatum* (chamise, "greasewood")

The most common shrub in the chaparral. Insect pollinated but some pollen is carried by the wind. Pollen morphologically like that of eucalyptus but smaller.

*Adenostoma sparsifolium* (red shanks)

Eastern slope of the mountains. Pollinates later than chamise. Less abundant.

## POLLINOSIS—HARSH ET AL.

### *Leguminosae* (pea family, legumes)

*Acacia* (sps.) (acacia tree)

Greatly over-rated as a cause of pollinosis.

### *Euphorbiaceae* (spurge family)

*Ricinus communis* (castor bean, castor oil plant)

May be of some local importance especially if near the patient's bedroom window.

### *Anacardiaceae* (sumac family)

*Rhus* (sps.) sugar berry, lemonade berry, etc.

Unimportant.

*Schinus molle* (pepper tree, Peruvian mastic tree)

Insect pollinated but much pollen is carried by the wind also. Dioecious.  
(The trees with berries are harmless).

### *Rhamnaceae* (buckthorn family)

*Ceanothus* (wild lilac)

Not a true lilac. Insect pollinated. Unimportant.

### *Myrtaceae* (myrtle family)

*Eugenia* (sps.). Unimportant.

*Eucalyptus* (sps.). Insect pollinated.

### *Oleaceae* (olive family)

*Ligustrum* (sps.) (privet). Occasionally of some local importance.

*Olea europea* (olive tree). Quite important. A transitional form between insect- and wind-pollinated forms.

### *Plantaginaceae* (plantain family)

*Plantago lanceolata* (English plantain). Slight importance.

### *Caprifoliaceae* (honeysuckle family)

*Sambucus caerulea* (blue elderberry). Questionable.

### *Compositae* (composite or sunflower family)

*Astereae* (aster tribe)

*Solidago californica* (California goldenrod)

Insect pollinated.

*Baccharis sarothroides* (chaparral broom)

The pollen closely resembles ragweed microscopically.

*Ambrosiae* (ragweed tribe)

*Hymenoclea monogyra* (desert fragrance, single-whorled burrobrush, jecote)

Abundant in Mission Valley and other river valleys near San Diego.

*Ambrosia psilostachya* (western ragweed)

Roadsides and waste places throughout the county.

*Franseria acanthicarpa* (*Gaertneria* a.) (false ragweed, bur ragweed, false western ragweed, prickly ragweed)

Mission Valley and along the road from Buckman Springs to Jacumba.

*Franseria bipinnatifida* (*Gaertneria* b., *F. Lessingii*) (beach bur)

Abundant on the beaches all along the coast. Much ambrosia-like pollen occurred on the slides at Alpine in the spring which could only come from this species even though thirty miles away.

*Xanthium pennsylvanicum* (*X. canadense*) (cocklebur)

Common in low places.

*Anthemideae* (mayweed tribe)

*Artemisia tridentata*, *angustifolia* (*A. angusta*) (sagebrush, black sagebrush, wormwood, "sage")

Sagebrush should not be confused with sage which has nothing to do with pollinosis. Abundant from Descanso to Jacumba.

*Artemisia californica* (coast sagebrush, hill "sage." California sagebrush, old man, wormwood)

Dominant shrub of hills and mesas near the coast. Pollinates very heavily for four or five days about three weeks after the first good rain in the fall. In the past seven years this period has come as early as October and as late as December.

*Artemisia dracunculoides* (Indian hair tonic, dragon sagewort, green sagebrush, tall wormwood)

Occasional roadside weed.

*Artemisia Douglasiana* (*A. vulgaris*, *A. heterophylla*) (mugwort, Douglas sagewort)

Along streambeds. This species has evidently declined in importance, probably due to the drying up of streams as a result of the construction of dams. Earlier writers classed this species as the most important cause of fall pollinosis in southern California. This is certainly not true now.

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AN INTRADERMAL TEST FOR THE RECOGNITION OF HYPERSENSITIVITY TO THE SULFONAMIDE DRUGS. Leftwich, W. B., Bull. Johns Hopkins Hosp., 74:26, (Jan.) 1944.

Reports of sulfonamide sensitivity have varied from 2 to 36 per cent. Sulfathiazole is more prone to produce sensitization than are the other members of this group of drugs. Previous attempts to determine sulfonamide sensitivity prior to clinical administration have been unsuccessful. The present report is a study of seventy-six patients, thirty-eight of whom were thought to be clinically hypersensitive (eight were questionably so) and the remainder of the patients served as controls. Blood was withdrawn from patients who had been under treatment with one of the sulfonamide group for a period of at least five days, and whose blood level varied from 2 to 20 per cent mgm. This blood sample was checked carefully to assure sterility and a negative serology. A blood level below 1.5 mgm. per cent was found to be unsatisfactory for this investigation as was the serum from those patients who had been receiving the drug for less than five days. An intradermal skin test with this serum was compared to a serum control test injected at the same time. Reactions were of the immediate type, with no instance of delayed reaction. A total of twenty-one patients were found to be sulfathiazole sensitive; four were sensitive to sulfanilamide, three to sulfadiazine, one to sulfapyridine and four to sulfamerizine. This corroborates the statement relative to the frequency of sulfathiazole sensitivity. Of the thirty definitely hypersensitive patients, positive skin reactions were obtained in twenty-eight. In the control group only two showed positive reactions on skin testing. In only three of twenty-five hypersensitive patients were positive reactions noted to sulfonamides other than the offending drug. This shows that the skin test is relatively specific for the individual sulfonamide drugs. Skin tests on persons who had never received sulfonamide therapy gave negative reactions in twenty-seven of twenty-eight tests. The sensitizing antigen may be a sulfonamide plasma protein combination, occurring in the circulation of patients under treatment, the sulfonamide acting as a haptene. Hepatitis and hemolytic anemia as a result of sulfonamide therapy are thought by the author to be on a toxic rather than an allergic basis as two patients with these conditions failed to demonstrate positive skin test reactions.

Bibliography. L.J.H.

## SOAP, SOAP SENSITIVITY AND SOAP SUBSTITUTES

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SOAP, which is the most universal, most successful, and psychologically the most acceptable of all detergents and cosmetics, is also one of the most ancient, its manufacture being described by Pliny and known before his time. Its many uses for toilet, household and industrial purposes probably make it also the most frequent skin contactant and, therefore, non-irritating as it may be to the majority of mankind, nevertheless one of the most common mild irritants. Used in normal amounts and on normal skin, soap rarely causes irritation but occasionally, because of its composition, chemical reactions or sustained use, its irritant qualities may cause a primary dermatitis. When the skin is abnormal, as in atopic eczema, it may act as a secondary exacerbating factor. The present paper concerns itself with a short history of the manufacture of soap, its chemistry, the nature of its action, the cause of its occasional deleterious effects, its germicidal activity, and the composition and use of some of the common soap substitutes.

In the days of Pliny (23-79 A.D.), soap was made by boiling goat tallow with beech ashes. The resulting soft potash-soap was treated with salt, becoming converted to a hard soda-soap. In later years, the wood ashes were replaced by soda ashes from seaplants and kelp, and in the thirteenth century, olive oil was substituted for tallow. In the eighteenth century, manufactured alkali began to be used, and later, coconut, palm and other oils, of which the most important constituents are: stearic, oleic and palmitic acids. At the present time, any oil may serve. Those of animal origin are tallow and grease, while those from vegetable sources include: coconut, palm, olive, castor, cottonseed, corn, linseed, and soya bean oils. The usual alkalis are: sodium, potassium hydroxide, and sodium carbonate, the reaction of the fatty acid and the alkali forming the salt of the fatty acid and glycerin.

In addition, among other substances, soaps may contain: potassium carbonate, trisodium phosphate, tetrasodium pyrophosphate, sodium sulphate, sodium silicate, calcium carbonate, persulphates and perborates, acid magnesium metasilicate (talc), barium hydroxide (barytes), ammonium hydroxide, rosin, essential oils, glycerin, starch, alcohol, sugar, organic and inorganic dyes, asbestos and kapok fibres, the last of these acting occasionally as an allergen in its own right.

Soaps may be medicated with sulphur, mercury, zinc, copper and lead, or with phenol, cresol, ichthyol and thymol. Although questionable in medicinal effects, soaps containing, among others, the following primary irritants

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are available commercially and used by patients: benzoin 5 per cent; boric acid 5 per cent; ichthyol 5 per cent and 10 per cent; phenol 1 per cent and 2 per cent; tar 3 per cent; resorcin 3 per cent and 5 per cent; salicylic acid 3 per cent; sulphur 5 per cent and 10 per cent; camphor 5 per cent; balsam of Peru 3 per cent; mercuric cyanide; metaphen; and organic dyes, bactericidal in action.

In industry, lime soaps form part of lubricating greases. The oleates, linoleates and resinates of the heavy metals, as aluminum, lead, cobalt and manganese, are used in paints, varnishes and water-proofing materials. Any of the above listed substances may, of course, act as primary or secondary, external or internal, irritating agents.

Since soap is hydrolized by water, the solution contains a precipitated acid or sodium hydrogen salt of the fatty acid together with small quantities of both the alkali and the free fatty acids. The water solutions are electrolytic conductors, and have been postulated by McBain<sup>27</sup> as containing "multiple charged, heavily hydrated, colloidal aggregates of ionized molecules." An alcoholic solution of soap acts as an unhydrolized, non-electrolyte.

Soap was originally thought to act because of its alkalinity. Spring<sup>48</sup> feels that soap acts as a "colloidal absorption compound." The extraneous material or dirt is given a lowered surface tension, and is therefore re-deposited with difficulty, being easily washed away. Particles of dirt may also be lubricated, made less adherent, dissolved and emulsified. Lewkowitsch and Warburton<sup>25</sup>, in their excellent article, give the ideal cleansing concentration as a 0.25 to 0.5 per cent solution.

Many studies on the deleterious effects of soap on the skin have been done. These may be classified into three groups. The first, rarely reported, is the individual who, requiring soap in ordinary amounts, responds with skin irritation and does his best to limit his use of soap to a minimum. The second group includes housewives and launderers who may use soap a great deal in their work, or whose work requires the use of a strong, harsh or abrasive soap for purposes of cleanliness. The last group is limited to those whose exposure to soap may be great since they are concerned in its manufacture.

Jordon, Dolce and Osborne<sup>15</sup> report on 239 instances of soap dermatitis in housewives and domestics. The skin condition improved in the warm months (when the skin was more acid), and during vacations. Patch tests were unsatisfactory because the materials were irritating, although in dilute solutions. Rabeau and Ukrainczyk<sup>36</sup>, in a study of occupational dermatitis in laundresses, have shown that the skins of 90 per cent of them lacked the capacity for neutralizing alkali and at a level found in only 8 per cent of normal individuals. That the subject is controversial can be judged from the work of Klauder<sup>19</sup> and his associates who believe that the soap is itself not irritating but that the essential oils, perfumes, dyes and rosins are the allergenic ingredients. Sulzberger<sup>51-53</sup>, on the other hand,

states that almost any soap will give a positive patch test if applied for twenty-four hours in a solution stronger than 2 per cent. Such reactions, he says, are not allergic since they are paralleled by alkaline solutions of equal strength, and are due to the reduction of the normal capacity of the skin for neutralizing alkali.

Gattefosse and his collaborators<sup>11</sup> studied the skins of those of their patients who suffered from dermatological conditions, and divided them into three groups. For the first of these, the diseased areas were alkaline in reaction while the remainder of the patients' skin was of normal acidity. The second group consisted of patients in whom the skin, both healthy and diseased, was alkaline. The third group presented healthy and diseased skins abnormally low in pH, that is, acid. The pH of the skin was determined by colorimetric methods, using chlorothymoid blue as indicator. A drop of this material in contact with the epidermis or mucous membrane, or mixed with the secretions being examined, indicated a pH range of 5 to 7.5.

The dermatological preparations used in the treatment of these patients were made in accordance with the reaction of the patients' skin, acid mycoses being treated with a triethanolamine stearate preparation, the pH of which was 7.5.

Edwards<sup>8</sup> tested the skins of human subjects with 0.0225 M solutions of pure and commercial soaps for four hours. Any irritations lasting more than two hours after the test was considered a positive reaction. His paper listed fifty-six soaps in order of irritating properties, and concludes that potassium soaps are more irritant than calcium soaps. Soaps made with lauric and myristic acids are more irritating than those made with pure acids.

Jordon and his associates<sup>15,16</sup> performed 2,300 patch tests on 150 patients with eight widely-used toilet soaps, and two laundry soaps, in dilutions of 1:100 and 1:400. Fifteen of the patients with normal skins reacted to the dilute soap solutions. Jordon stated, therefore, that a positive patch test does not always signify a sensitivity to the substance causing it. On the other hand, approximately 50 per cent of those patients who presented dermatological lesions, reacted to the dilute soap solutions. Seven individuals with other forms of allergy gave four instances of reactions. The author feels that a mild erythema without papules or vesicles is not to be regarded as a positive reaction. He is of the opinion also that the alkaline content of the soap is of minor importance in the production of eczema; and that the fatty acids and other miscellaneous ingredients of the soaps are the most likely etiological factors.

Kooyman and Snyder<sup>21</sup> discuss methods devised especially for the measuring of small differences in the mildness of soaps. They say that since soap is used in such large quantities, with so low an incidence of irritation, that it must be a very mild primary irritant. Secondary factors which produce hyper-irritability may include dry, ichthyotic skins and such environ-

mental factors as prolonged exposure to the sun, wind or cold and dry atmospheres. Controlled patch tests can, therefore, detect small differences in intensity of reaction. Of each soap solution, 2 c.c. are used to moisten the patch. The authors feel that the concentration of the soap should be great enough to produce some reaction; and had their greatest success in achieving such reactions with solutions containing 8 per cent by weight of soap. Under these conditions, the greater number of the subjects had a slight to moderate erythema after six hours of exposure. Soaps made largely from coconut or similar oils were more irritating than other toilet soaps. The test was able to magnify the effects of soap sensitivity objectively, and within a short period of time, the slight differences being of extreme importance to certain patients and under certain conditions.

Blank<sup>4,5</sup>, at an earlier date, had discovered that the saturated fatty acids of low molecular weight gave more positive patch tests than those of higher molecular weight, and that the fatty acids in castor oil rarely gave positive patch tests. The higher the molecular weight of the fatty acids, the more alkaline must the skin be before the onset of irritation.

References to occupational dermatoses are many and voluminous. Excellent papers by Schwartz<sup>41-46</sup>, Sulzberger<sup>51-53</sup>, Klauder<sup>10,20</sup>, Hall<sup>13</sup> and Whitwell<sup>56</sup> discuss the incidence of occupational skin disease, stressing over and over again the rôle played by cleansing agents including soap which, in many cases, is the prime irritant.

The problem of soap dermatitis has also been worked upon from the point of view of the skin. Markowitz<sup>26</sup> masterfully summarizes the available literature, stressing the high acidity (pH 5.3) of the surface of the epidermis excepting "the scalp in children, and in adults the axilla, genitocrural folds, anal regions, interdigital spaces and portions of the soles." Blank<sup>4,5</sup> found the antecubital region the most acid area on the arm, and Pillsbury and Shaffer<sup>33</sup> the fourth interdigital space of the foot the least acid area of the skin surface. They demonstrated that acid solutions applied to the skin had little tendency to rise in pH, but that alkaline solutions showed a definite and regular drop in pH. They conclude that a standard patch test is an inefficient means of maintaining the concentration of any applied solution.

Markowitz<sup>26</sup> quotes Marchionini as saying that alkalinity of the skin, by favoring coagulability of the colloids of the keratin layer of the epidermis, reduces their stability and resistance, and this, with the fact that certain bacteria and fungi thrive best in alkaline media, explains the frequency of microsporon infection in the scalps of children, of abscesses in the axillae of adults, epidermophyton inguinale and the yeast infections in the genitocrural and anal regions and the epidermophytids in the interdigital folds and certain parts of the sole.

Arnold<sup>1</sup>, in a study of the relationship between certain physical-chemical changes in the cornified layer and the endogenous flora of the skin, demonstrated that the exogenous bacterial flora residing on the surface of the



skin can be increased by alkalinization and by exposure to warmth. The same flora can be decreased by exposure of the skin to acid. The cornified layer behaves like a colloidal gel structure, an increase in water content causing an increase in the surface endogenous flora. Dehydration of this layer causes a decrease in the viable bacteria of the surface. The flora return to the normal density when the cornified layer readjusts itself, this adjustment requiring thirty minutes after alkalinization and about two hours following acidification. The survival of the exogenous bacteria follows the same pattern, the increased water content of the cornified layer permitting exogenous bacteria to survive for longer periods of time. A dehydrated cornified layer rapidly renders bacteria non-viable.

Since soap is frequently used as a bactericidal agent as well as for cleansing, there are many studies concerned with these properties of soap itself. In this field also there is a lack of unanimity. In 1927, Barber and Noble<sup>3</sup> found soap and water fully germicidal for *Staphylococci*, *E. coli*, and *B. subtilis*. On the other hand, Eggerth<sup>9</sup> studied the effects of pH on the germicidal action of soap showing that it varied with the organism used. Walker<sup>55</sup> stated that ordinary soap solutions of a concentration of 0.4 to 0.6 per cent were equal to phenol 0.5 to 1.0 per cent, and rapidly killed staphylococci, meningococci, gonococci, pneumococci and diphtheria bacilli, while the bacteria of typhoid, paratyphoid and dysentery were killed by moderate concentrations of soaps made with saturated fatty acids.

Prescott and Riley<sup>35</sup> found each soap more effective against some bacteria than against others. Davison<sup>7</sup> showed that soaps of high detoxifying ability and ready diffusion were highly germicidal as they were correspondingly poor surface-tension depressants.

In more recent years, there has been a complete reversal of this point of view. Klarrman and Shternov<sup>18</sup> answer the query, "Are soaps germicidal?" by testing sixteen potassium, seven commercial, and six saponified fatty-vegetable oil soaps against: *Staphylococcus aureus*, *Streptococcus haemolyticus*, *Eberthella typhosa*, *Shigella paradysenteriae* and *Trichophyton rosaceum*, by the Food and Drug Administration methods, and found commercial soaps not germicidal. Pohle and Stuart<sup>34</sup> report, however, that some soaps will kill the organisms removed from the skin and that rosin soap used for one week reduces both residual and transient flora. Used at a pH of 10.2 and at 30° C., rosin soaps will kill *Staphylococcus aureus*, *Eberthella typhosa* and *Enterococcus coli*. Reasoner<sup>37</sup> some years ago apparently demonstrated the lethal effect of soap on the *Treponema pallidum*, and more recently Stock and Francis<sup>39</sup> have shown that soap inactivates the virus of influenza.

Notwithstanding the germicidal effect soap is supposed to have, germicides have been added to soap in an attempt to sterilize the skin. The history of these mixtures has invariably followed the same pattern. The material when in soap was not germicidal, and often caused a primary irri-

tation. The most recent, and probably the most promising, is described by Traub and his collaborators<sup>54</sup> who used a new synthetic phenol, designated as G-11. This compound, in soap, was found to be non-irritating to the skin as judged by more than 200 patch tests, repeated on the same subjects, ten to fourteen days later with negative results. Subjects using a 2 per cent solution regularly for one year showed no evidence of irritation. The regular use of the compound resulted in a lower residual count after two minutes of washing than could be achieved after twenty minutes of washing with ordinary toilet soap. The author concludes that a surgeon, or operating-room attendant, using this compound, could maintain an extremely low bacterial population of the skin, and perhaps shorten the pre-operative "scrub-up" procedures as well as eliminate the use of irritating germicides.

If soaps are germicidal, their effects may depend either on their composition or the changes they cause in the skin. From the work of Jones and Lorenz<sup>14</sup> it would appear that calcium soap actually facilitates the production of staphylococcal infections since calcium ions, when present in an oil-water mixture, enable the contained bacteria to pass more easily into the oily layer and so into the follicles and the sebaceous glands; the bacteria being viable for at least two weeks in calcium soap precipitates.

Pillsbery, Livingood and Nichols<sup>32</sup> state that it is the mechanical cleansing of the skin which is the effective means of reducing its bacterial inhabitants, being an important part of treatment of any superficial pyogenic infection. They go on to say that the strength that is ordinarily used in washing with commercial fatty-acid soaps is not antiseptic, and that the mechanical action of washing and scrubbing plays the more important part in lowering the bacterial counts. Potassium permanganate, boric acid and aluminum acetate were relatively ineffective in reducing the bacteria flora, suggesting that the solutions act by softening the skin so that the bacteria are more easily removed by washing and by other means. Arnold and his colleagues<sup>1</sup> feel that there is still another type of inter-relationship. The bacteria not killed by soap may be more easily killed by clean skin than by that which is dirt-contaminated. They discovered that although dirty skin had slight germicidal powers against *Salmonella enteritidis*, clean hands rapidly destroyed this test organism. For a general survey of soap in medicine, a recent article by Lesser<sup>23</sup> should be consulted. For an earlier, well-balanced discussion, that by Fantus<sup>10</sup> is generally available and well worth reading.

It should be mentioned that soap is also used for other purposes than for cleansing and germicidal activity. In 1937, Nolan<sup>29</sup> described a method of using sulphur soap paste in the treatment of scabies. The material known as Sulphurfoam is widely used as a scabicide, the lather containing sulphur being permitted to dry on the skin, and renewed at the end of twenty-four hours. The patient with sensitivity to either soap or sulphur may react adversely to this treatment. More recently, Gordon and his col-

leagues<sup>12</sup> have used soap impregnated with tetra-ethylthiurammonosulphide—"Tetmosol." In eighty-eight of 110 men given three baths with 20 per cent "Tetmosol" in soap, the scabitic infestation was completely eliminated. In twenty-two patients, there was a relapse. Of 242 men given "Tetmosol" vaths, four developed a dermatitis, patch tests being negative in three of the positive reactors. It is difficult to evaluate in these patients whether the sensitivity was to the scabicide or to the soap.

Although not entirely pertinent to the present discussion, attention is drawn to a paper by Stokes, Lee and Johnson<sup>50</sup> on contact, contact-infective, and infective-allergic dermatitis of the hands. This paper represents a thoughtful analysis of 200 patients studied over a period of ten years, and discusses in detail the treatment of these coincident dermatitides of the hands of which soap sensitivity is only one part. The paper is unusual in its acceptance of the patient as an individual rather than as a case of dermatitis. Treatment is preventive and constitutional as well as local. To support the conviction that "disabled hands express bodily dysfunction preparing the way for, or reinforcing specific insult," the author concludes that "only by the broad, in combination with the detailed, approach can cause, treatment and the best prognosis the circumstances warrant be aligned on a sound foundation."

However controversial the literature may be on the cause or amount of soap sensitivity, the condition frequently exists and often complicates skin lesions not directly due to soap sensitivity. These must be recognized and treated, preferably prophylactically. The number of soap substitutes and the great amounts in which they are used prove how acute is the problem. Unfortunately, for hand cleansing, the ideal soap substitute has not yet been prepared, although some preparations are more satisfactory than others.

Schwartz<sup>41-46</sup> describes a sulphonated castor oil (pH 7.2) containing a wetting agent. The material has been used successfully, not only for cleansing, but also in patients in whom soap and water are contraindicated as in the treatment of atopic eczema in young children. Burkhardt<sup>6</sup> advocates a similar preparation. Reuter<sup>39</sup>, who lists a number of skin-protective ointments, suggests the use of a cleansing solution consisting of equal parts of sulphonated Neat's foot oil and mineral oil with gelatin 25 per cent added to white granulated corn meal, the proportion being 2:3.

Lane and Blank<sup>22</sup> used sulphonated oils for 279 patients of whom 87 per cent improved and 8 per cent grew worse. Positive patch tests were given by 1 per cent. The patients' conditions relapsed when they returned to the use of soap. Rogers, Cohen and Goldberg<sup>40</sup> used sulphonated oils in

the treatment of burns. The formula of their recommended preparation contained:

Paraffin and wax.....	265.00
Sulphonated mineral oil.....	330.00
Sodium laurel sulphate.....	10.00
Sulphonamide .....	50.00
Triethanolamine .....	100.00
Water .....	30.00

Mummery<sup>28</sup> discovered that the use of a neutral sulphonated castor oil in 2 per cent wetting agent, as a substitute for soap, decreased soap reactions from 12.5 per cent of 3,714 subjects to 5.7 per cent of 3,435 factory workers, and from 14.2 per cent of 572 to 3.5 per cent of 523 machine shop workers following its use for one year. The subjects were exposed to: paraffin, machine oil, cutting grease, and a number of chemicals which remove the oil present in normal skins. Extended use of the material left the hands soft, clean, and comfortable.

A number of authors suggest that the hands be placed in acetic acid 3 per cent after washing, in order to return its acid properties to the skin.

The most complete recent review (June, 1943) appeared in the *Journal of the American Medical Association*. It lists the thirteen formulas for protective creams and cleansing agents reported by Klauder<sup>19,20</sup> and the protective applications described by Schwartz.<sup>41-46</sup>

The difficulties attendant upon the use of these preparations are mentioned by Sharlit<sup>47</sup> who is critical of soap substitutes since they contain wetting agents which increase the permeability of the keratin surface of the skin and also hydrophilic oils which are occasionally irritating. Neither is psychologically satisfactory. He suggests the use of super-fatted soap containing at least 10 per cent of free vegetable oil. Kile<sup>17</sup> suggests a practical solution, reporting on fifty-seven young women who used two soaps identical excepting for the super-fat content. Of the subjects, 86 per cent reported no discomfort of any sort with either soap. For the super-fatted soap, two registered some discomfort, but for the control soap, this number reached 12 per cent. Thirty per cent found no difference in the drying effects of either soap but 54 per cent found the super-fatted soap less drying than that which was not super-fatted. It appeared that the subjects with dry skins preferred the super-fatted soaps. Subjects with oily or normal skins seemed to prefer the control soap. Kile suggests that the soap may act by removing less oil from the skin than ordinary toilet soaps do, or perhaps that additional fat is left as a residue on the epidermis.

Sulzberger<sup>51</sup>, commenting editorially on a paper by Lane and Blank<sup>22</sup>, mentions the fact that the patients complained of a "dryness" of the skin following the use of soap substitutes. That this dryness is not an irritation was shown by Parkhurst<sup>51</sup> who patch-tested patients with the oily residue left on the skin by sulphonated oils and sulphonated alcohol, and re-

ported that they were not irritating, giving negative patch tests. In our own experience with patients suffering from soap sensitivity, this criticism is one of psychological value that the patient does not see the dirt removed and says that his hands and his body do not feel "clean."

Acidolate (National Oil Products) is one of the commonest used, commercially available sulphonated oils, described as being completely water-miscible independently of the temperature or the hardness or softness of the water. Containing fatty acids and of high molecular weight, it has emulsifying properties for both fat-soluble and water-soluble skin detritus. Its pH is 6.25 and approximates that of normal skin, and it therefore causes no alkaline reaction. Many of our patients are so accustomed to a lathering skin-cleansing material, however, that they object to any non-lathering skin detergent as a matter of habit and training.

A soapless detergent consisting of propylene glycol, propylene glycol esters, and sorbitol with a pH of 6.8 has proved quite satisfactory. No reports of sensitivity to this material have been recorded.

Of the lathering soap substitutes in cake form, two have recently been offered to physicians.

The first of these consists of lauryl sulphoacetate, diluted in betonite; the lather having a pH of 5.0 to 5.5. This soap is described as being non-irritating, and of low sensitizing index. Those of our patients for whom it was prescribed claimed that it was not an effective substitute for soap, although its cleansing properties were excellent. Their objections were purely psychological in type, but nevertheless firm.

On the other hand, six patients given the second soap substitute, which consists of sodium p-ter-octyl-phenoxy-ethoxyethoxyethyl ether sulphonate, lanolin, cholesterol and petrolatum, all remark on its efficacy. The material lathers, is emollient and detergent, with a pH of 5.5, being active in all types of water, including sea water. This preparation has only recently become available; no reports of sensitivity have so far been described.

It is apparent from this review, which is by no means complete, that soap sensitivity is an extremely complex phenomenon. Soap may cause irritation by nature of its primary or secondary constituents, or by its alkalinity, on skins which may be primarily or secondarily irritable by reason of their physiological condition, their allergic potentialities, concomitant disease and degree of exposure. Since the skin maintains its homeostasis, the changes in pH of the patch tests vary with the time of exposure. In addition, since the pH of the skin itself varies from site to site, this reaction is not constant. The evaluation of a positive patch test to soap is therefore difficult. The test itself is rarely dependable.

Soaps which are used for other purposes than cleanliness expose the patient to risk of additional irritation. Soapless detergents are available but none, as yet, is as satisfactory as soap.

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THE TREATMENT OF ASTHMA AND HAY FEVER. Robert A. Cooke, *New York State J. Med.*, 43:1225, (July 1) 1943.

This comprehensive clinical review, though not directed particularly at the pediatrician, is very helpful because, in general, any therapeutic measure which will alleviate allergic conditions in adults will also be useful for infants and children. In view of the tendency of some pediatricians to discount casein as a cause of allergic manifestations, the brief case report of a physician with nasal allergy due to the ingestion of casein is most interesting. Atopic asthma is the type most frequently encountered in infants and children and young adults, and its onset is rare after the age of forty; infectious asthma may occur at any time from infancy to old age. Children up to eighteen years need little attention to the sinuses, if recurring infections can be controlled. The early removal of infected tonsils and adenoids is one of the best means of control. As sedatives in asthma, appropriate doses of codein or pantopon may be given children when necessary. If these drugs produce vomiting at first so much the better, for it is more effective than coughing in removing mucous plugs. For the definite purpose of producing vomiting in children, however, syrup of ipecac in doses of  $\frac{1}{2}$  to 1 teaspoon may be given.

J.G.

## REPORT OF A CASE OF SPONTANEOUS ANIMAL ALLERGY

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THE use of the terms *allergy* and *atopy* remains controversial when applied to the phenomena of altered specific reactivity occurring in lower animals. This additional report to previous literature on the subject should aid in a proper terminology.

The terms *allergy* and *hypersensitiveness* are used interchangeably to indicate all forms of acquired and specific altered reactivity in humans or in lower animals from that of the normal.

The authors agree with Sulzberger and others that, for instance, asthma, produced by quinine, is an allergy, whereas production of tinnitus by a dose of this drug, ordinarily not causing symptoms, would be an exaggerated response or hypersensitiveness. They also accept Forman's classification of allergic sensitivity as modified by Sulzberger and Coca's classifications of atopy.

However, after considering cases, such as reported by Wittich and his co-workers, and the facts herein reported, it is possible to give a new interpretation to Coca's concept of allergy.

Coca states in his classical manual (1933) that atopy means "certain clinical forms of human hypersensitiveness that do not occur so far as is known in the lower animals and which are subject to hereditary influence." We think that Coca has not denied the possibility of applying the word atopy to lower animals, since he did leave this possibility in his definition for the future, when the clinical form of hypersensitiveness, meaning quantitatively increased reactivity, may be proven to exist in lower animals.

From Coca's definition one does not infer that the lack of hereditary antecedents may be an element of fundamental judgment to discount a diagnosis of atopy. According to Ruiz Moreno's opinion, atopy is a diagnosis arising from a number of facts (mentioned by Coca) which in essence are the following:

1. Constitutional inherited conditions characterized as being fundamentally the result of smooth muscle spasm or Quincke type of edema.
2. Presence of personal conditions showing the same characteristics.
3. The clinical picture must be the result of the interaction between a substance like atopen, allergen or antigen with the specific antibody, as a consequence of prior tissue contact.
4. This reagin must be passively transferable and should not give reactions *in vitro*, such as precipitation or complement fixation.

The syndrome must be the result of a Quincke type of edema or smooth muscle spasm, in which one generally finds numerous eosinophiles either in the tissues, as in the blood, or in the secretions from



the affected organs. Moreover, epinephrine should be an efficient sympathomimetic remedy in almost all the cases. These last facts reinforce the diagnosis of atopy. They support the four fundamental characteristics as secondary features. Furthermore, the first two fundamental characteristics mentioned lose their importance to the patient since their presence is secondary to the other two conditions.

#### CASE REPORT

The present case under study is a Cairn terrier dog, called "Betty," three years of age, weighing 20 pounds. Not long after birth, and almost to complete development, a syndrome developed characterized by a generalized pruritus. This became worse with a subsequent simultaneous erythema which persisted. At the time of the examination only dermal scratch lesions were observed. The idea that these lesions might be due to Sarcoptidae was discarded. After some time, skin lesions were observed on a congested erythematous site which was characterized by the presence of scabs of various sizes, yellowish brown in color, which desquamated easily. These lesions were spread on the folds but mostly on the belly and genital and peri-anal regions. Red-brownish scabs were also found, these being interpreted as being merely scratching lesions. In general, the pink skin became deep red with isolated spots of healthy skin. About a year ago, two plaques appeared on the dorsal posterior region at each side of the tail. These were of rough appearance, blackish brown in color, hairless, about the size of a silver dollar, easily removed and were thought to be of parasitic (fungi) origin. After staining some slides from the scratched plaque and plating two Sabouraud Petri dishes, we could corroborate the mycological involvement already suspected.

There was present a perennial rhinopathy, characterized by sneezing and a slight watery discharge.

The symptoms suggested a non-human spontaneous allergy. Accordingly, intracutaneous tests with various allergenic extracts were done on the anterior, previously shaved, thoracic region. Pertinent food allergens and routine epithelium and dust extracts, each with a total nitrogen of 0.05 mg., were used.

Positive results were obtained with the following allergens: maize (slight reaction), oats (slight reaction), cacao (slight reaction). As far as the inhalants are concerned, the dust extract, in a tenfold dilution, produced a slight positive reaction.

Considering the results obtained thus far, we did not continue with the routine tests. After two hours, the animal showed a typical symptomatic reaction with pruritus, erythema and reactivated eczematous lesions. Moreover, there was a generalized thrill and increased pulse, as well as increased respiratory rhythm with dyspnea and oliguria for about twenty-four hours. All these conditions obliged the animal to keep resting, and whatever foods or drugs were provided were refused.

A dose of 1.5 mg. of epinephrine was administered by the subcutaneous route, injecting 0.5 c.c. of 1:1000 solution each time. The animal completely recovered by this treatment.

Since the preliminary skin tests to meats were negative, we prescribed a meat diet. After a week, the suspected allergic symptomatology was pronouncedly improved by the elimination diet given. Moreover, the local skin treatment with iodine resulted in the improvement of the skin lesions.

We then performed the clinical counterproof with positive results. In order to corroborate our presumption about this case of spontaneous allergy, we carried on some laboratory tests. The animal was bled and the passive transfer test in a normal dog was performed with the serum.

After forty-eight hours the presence of reagins in the serum of the dog under study was detected, since positive results were obtained after the same allergens were tested. Controls were negative.

Thereafter the serum was used for the detection of precipitins by two different methods as follows: 2.5 c.c. portions of serum in a series of three Kahn tubes were pipetted, to which 2.5 c.c. maize, oats and cacao extracts were added separately with a capillary pipette by the walls, each with a total nitrogen content of 0.05. Another series, using 2.38 of total nitrogen instead, was also set up, following the same technique.

Moreover, dust extract of two different concentrations, one being 1:10 of the second, was included in the first series of tests. With the same antigens and identical concentrations already mentioned, the following technique was used: 2.5 c.c. of allergen were pipetted first in the test tubes; then, the same amount of dog serum was added with a capillary pipette from the bottom. The whole set of tubes was observed after five, fifteen and thirty minutes, and no precipitation was noticed, even with the aid of a magnifying glass.

#### SUMMARY

The arguments which support our diagnosis of allergy in the lower animal, according to the terminology used by Coca and others, are the following:

1. The qualitative and quantitative acquisition of altered reaction.
2. The fact that the clinical picture is produced by nontoxic substances incapable by themselves of giving rise to the same symptomatology in the dog.
3. The curative action of an elimination diet, excluding the causative foods.
4. The fact that the administration of the causative foods gives rise to the above clinical picture.
5. The provocation of the clinical picture by the skin tests with extracts of the causative foods.
6. Diagnosis of anaphylaxis may be discounted, since we are dealing with a specific sensitivity spontaneously acquired, not proved by any treatment.

The supporting arguments for the diagnosis of atopy (atopy allergy) are the following:

1. Presence of transferable antibodies, other than precipitins (sensitizing antibodies).
2. Successful treatment with epinephrine.
3. The fact that we are dealing with a phenomenon due to the interaction of antigen and antibody.
4. Presence of smooth muscle spasm (dyspnea) and edema (rhinopathy and skin tests).
5. Positive skin tests with the causative food extracts.

#### CONCLUSION

This is one more case supporting the contention that the word atopy may be applied when referring to some forms of spontaneous allergy observed in lower animals.

# SERUM POTASSIUM RESPONSE TO EPINEPHRINE IN NORMAL AND ASTHMATIC SUBJECTS

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SERUM potassium determinations on normal and asthmatic subjects have been made in an effort to demonstrate whether epinephrine given subcutaneously has any effect on serum potassium levels. There are conflicting reports in the literature regarding serum potassium response to epinephrine in normal human beings. Keys<sup>9</sup> found that intravenous injections over a period of 1.5 to 3 min. of 0.005 to 0.3 mgm. epinephrine hydrochloride in normal man produced an immediate marked fall in the level of plasma potassium with a return to a near normal level in twenty minutes. This was followed in forty to sixty minutes by a rise which was in most experiments significantly above the pre-epinephrine level. Brewer et al.<sup>2</sup> determined serum potassium values in seven adults before and after rapid intravenous injection of 1 cubic centimeter of epinephrine 1:1000 into the opposite arm. They found values from 17.9 to 18.2 mgm. per cent before injection with rises to 19.1 to 22.4 mgm. per cent thirty to ninety seconds after injection of epinephrine. These values are in line with those originally reported by D'Silva<sup>4</sup> in cat experiments in which the serum potassium rose more than 12 mgm. per cent above the original level one minute after intravenous injection of 0.05 mgm. epinephrine. Both Keys and Brewer were able to confirm D'Silva's results after rapid intravenous injection of epinephrine in dogs, cats, and rabbits. Flock<sup>5</sup> found the continuous injection of epinephrine caused a decrease in serum potassium from 19 to 32 mgm. per cent in dogs. This has been confirmed by Larson,<sup>10</sup> in cats and dogs by perfusion experiments.

Because, as Camp and Higgins<sup>8</sup> have pointed out, both potassium and epinephrine in man as well as in animals show similarity in physiological response, potassium salts have been rather widely used in the treatment of allergic diseases. Attempts have been made to modify the course of bronchial asthma and other allergic disorders by altering the potassium-sodium relationship either by oral administration of potassium salts or by changes in potassium content of diet.<sup>1,7,12,13</sup> The possible relationship between potassium metabolism and epinephrine action in asthma prompted the present study of the effect of epinephrine on serum potassium, using the drug in the doses and by the route in which it is so effective clinically.

## EXPERIMENTAL STUDIES

The following studies were made on serum from both normal and asthmatic subjects. The methods determining potassium were those of Strauss<sup>14</sup> and Harris.<sup>6</sup> All determinations were done in triplicate. Serum

From the Department of Pediatrics, Duke University School of Medicine and Duke Hospital, Durham, N. C. Presented at the First Annual Meeting of the American College of Allergists, Chicago, Illinois, June 10 and 11, 1944.

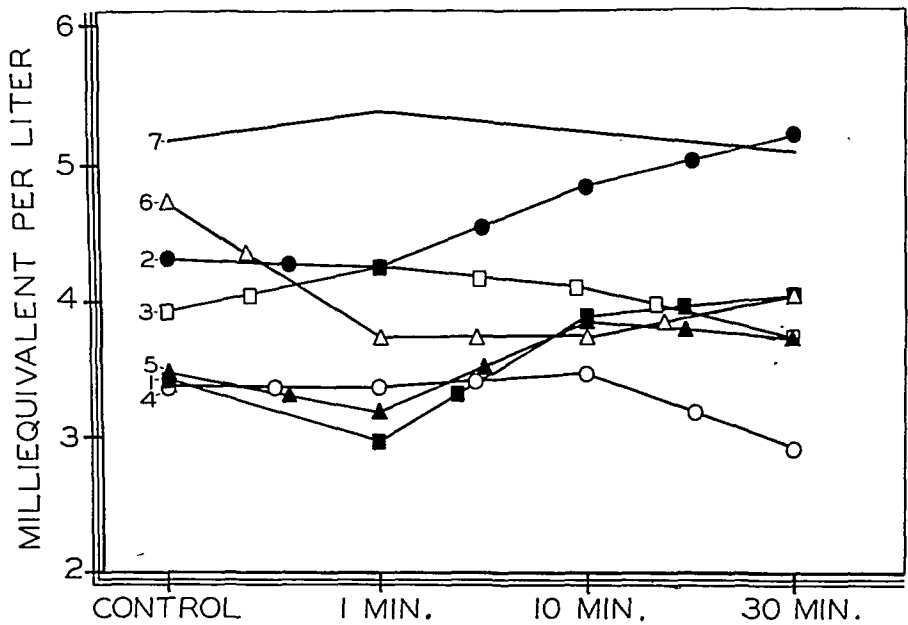
# SERUM POTASSIUM RESPONSE—DEES

TABLE I. SERUM POTASSIUM VALUES IN NORMAL ADULTS AFTER SUBCUTANEOUS-PHYSIOLOGICAL SALINE INJECTION

No.	Name	Control Meq.	1 Minute Meq.	10 Minutes Meq.	30 Minutes Meq.
1	M.G.	3.43	2.96	3.89	4.08
2	N.B.	4.32	4.27	4.87	5.23
3	D.R.	3.91	4.28	4.13	3.73
4	A.M.	3.37	3.37	3.49	2.91
5	D.B.	3.49	3.19	3.85	3.73
6	O.A.	4.71	3.73	3.73	4.07
7	H.V.	5.19	5.40	5.28	5.10
	Mean	4.06	3.89	4.09	4.12
	S.D.	0.71	0.84	0.76	0.81

CHART I

SERUM POTASSIUM VALUES IN NORMAL ADULTS AFTER SUBCUTANEOUS PHYSIOLOGICAL SALINE INJECTION



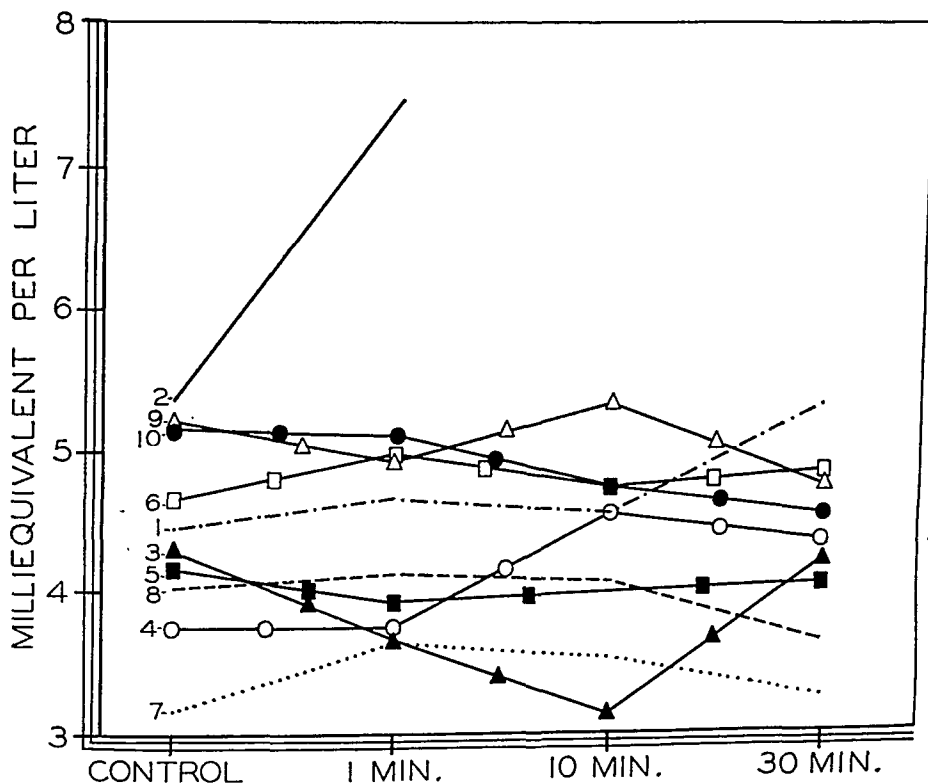
potassium was determined on twenty-eight adults, eleven of whom had bronchial asthma. All subjects were either fasting or had been without food for at least six hours. The blood specimens were drawn before, and one, ten and thirty minutes after the rapid subcutaneous injection of 0.75 c.c. epinephrine hydrochloride 1:1000 into the opposite arm. The same amount (0.75 cubic centimeter) of physiological saline was used as a control injection. All subjects receiving adrenalin exhibited a rise in systolic blood pressure from 20 to 30 mm. Hg. with increase in pulse rate of

at least twenty per minute, one minute after the injection. Several patients with bronchial asthma, who were having attacks at the time of the experiment, showed transient relief of respiratory symptoms. The sera were divided into three groups (1) normal subjects after physiological saline, (2) normal subjects after adrenalin, and (3) asthmatics after adrenalin.

Table I shows the serum potassium values in the normal subjects receiving physiological saline injections, together with means and standard deviations for each time interval. Figure 1 shows a composite graph of these potassium values expressed as milliequivalents. Table II and Figure 2 give similar data for serum potassium after the injection of epinephrine

CHART II

# SERUM POTASSIUM VALUES IN NORMAL ADULTS AFTER SUBCUTANEOUS EPINEPHRINE INJECTION



in normal subjects. The serum potassium values for the asthmatic patients before and after injection of epinephrine are given in Table III and Figure 3. Table IV shows the mean differences with their standard deviations for serum potassium values before and after injections in all three groups. In every case the standard deviation exceeds the mean difference, which therefore is without significance.

## DISCUSSION

From these experiments it is shown that the subcutaneous injection of 0.75 c.c. of epinephrine 1:1000 does not produce any significant alteration

# SERUM POTASSIUM RESPONSE—DEES

TABLE II. SERUM POTASSIUM VALUES IN NORMAL ADULTS AFTER SUBCUTANEOUS EPINEPHRINE INJECTION

No.	Name	Control Meq.	1 Minute Meq.	10 Minutes Meq.	30 Minutes Meq.
1	S.D.	4.48	4.67	4.55	5.33
2	S.W.	5.39	7.46		
3	S.W.	4.30	3.69	3.15	4.22
4	J.D.	3.75	3.75	4.54	4.36
5	S.D.	4.18	3.94		4.06
6	E.L.	4.66	4.96	4.72	4.84
7	S.W.	3.15	3.63	3.51	3.27
8	H.V.	4.02	4.11	4.06	3.65
9	M.F.	5.22	4.93	5.34	4.74
10	K.C.	5.18	5.13	4.73	4.57
	Mean	4.43	4.63	4.33	4.34
	S.D.	0.70	1.15	0.71	0.63

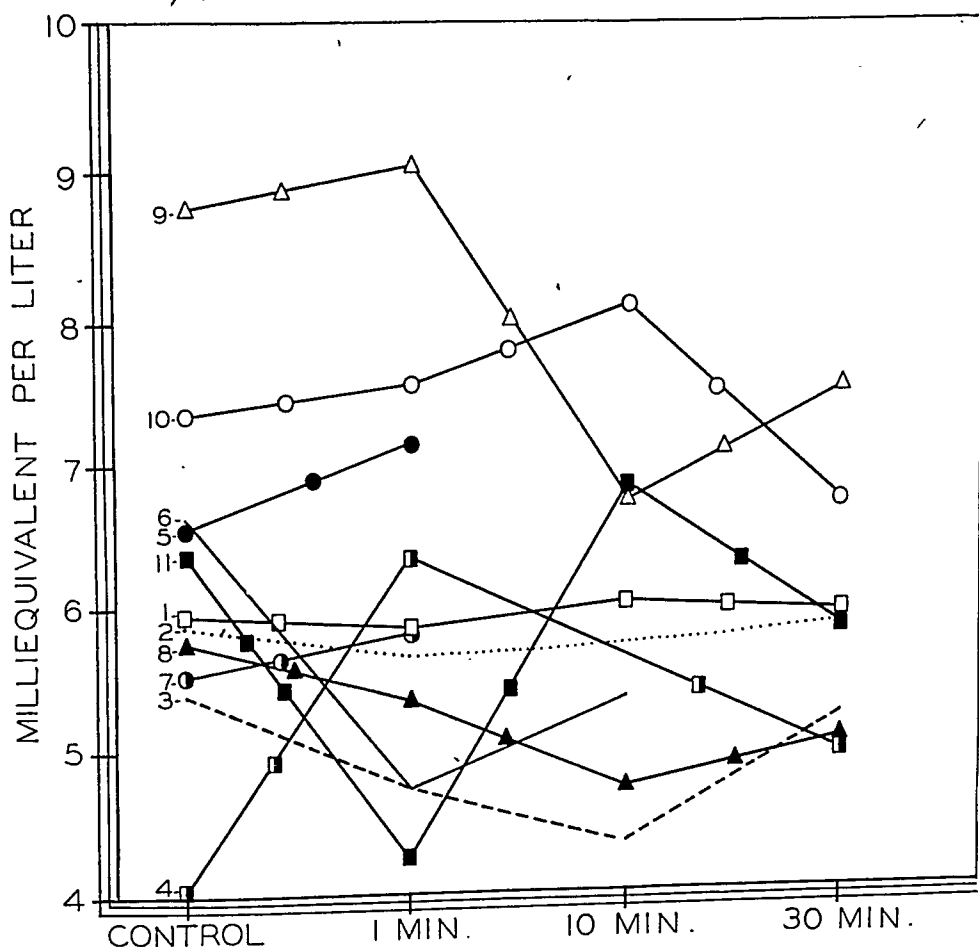
TABLE III. SERUM POTASSIUM VALUES IN ASTHMATICS AFTER SUBCUTANEOUS EPINEPHRINE INJECTION

No.	Name	Control Meq.	1 Minute Meq.	10 Minutes Meq.	30 Minutes Meq.
1	J.L.	5.95	5.87	6.05	5.99
2	F.P.	5.87	5.69	5.75	5.87
3	G.I.	5.39	4.73	4.31	5.33
4	M.S.	4.06	6.36		4.96
5	W.H.	6.54	7.15		
6	I.J.	6.61	4.73	5.39	
7	G.S.	5.51	5.84		
8	N.G.	5.74	5.35	4.73	5.09
9	G.A.	8.78	9.09	6.75	7.52
10	F.P.	7.39	7.58	8.12	6.73
11	J.McC.	6.37	4.24	6.87	5.87
	Mean	6.20	6.06	6.00	5.92
	S.D.	1.20	1.43	1.24	0.86

TABLE IV. MEAN DIFFERENCES BETWEEN CONTROL VALUES AND VALUES AFTER INJECTION, WITH STANDARD DEVIATIONS

	1 min.	10 min.	30 min.
7 normals-saline	-0.17±0.45	+0.04±0.51	+0.06±0.40
10 normals-epinephrine	+0.9 ±0.73	-0.02±0.56	+0.01±0.49
11 asthmatics-epinephrine	-0.11±1.22	-0.52±0.96	-0.27±0.36

CHART III

SERUM POTASSIUM VALUES IN ASTHMATICS AFTER  
SUBCUTANEOUS EPINEPHRINE INJECTION


in serum potassium levels, as obtained from venous blood. This is at variance with reports in the literature after intravenous injection of epinephrine of an immediate rise or fall in the potassium levels and with statements as to an ultimate rise after thirty to sixty minutes to levels above the pre-injection level. In spite of absence of demonstrable chemical change in potassium, all of the subjects receiving adrenalin exhibited the typical subjective and objective physiological responses to the drug. That there is a definite relationship between the electrolyte level of potassium and the injection of adrenalin seems well established in experimental animals, and for humans when the route of administration of the drug is intravenous. This relationship is not borne out in the present series of patients using the subcutaneous route of injection. The exchange of potassium from extracellular to intracellular fluid may occur too rapidly or be of too small magnitude to be detected by the technique employed in these determinations. The assumption that the pharmacologic effect of epinephrine is due to increased mobilization of plasma potassium cannot

be demonstrated when epinephrine is given subcutaneously to asthmatic or normal humans.

In the present series of analyses normal sera in the control period gave mean values for potassium of 4.06 and 4.43 milliequivalents per liter. The group of asthmatic patients had a mean value for serum potassium of 6.02 milliequivalents per liter. This difference, using pooled normal, has a  $t = 5.33$  for 27 degrees of freedom which is a highly significant difference. This finding is in accord with reports of Rusk et al.<sup>11</sup> and Jacobs<sup>8</sup> of elevated potassium levels in allergic states as compared to normals. However, the values obtained in the asthmatics presented here are somewhat higher, and the differences between them and the normal are greater than in the two series referred to above. The explanation for the high potassium levels in our series may be related to the severity of the asthma, as all the patients were hospitalized for treatment of "status asthmaticus." The more obvious sources of high potassium such as diet and medication can be eliminated as contributing factors, since all the asthmatics were on general diets and were receiving no additional potassium when the blood samples were drawn. Technical factors likewise can be eliminated since the samples from asthmatic and normal patients were obtained under the same conditions, and the determinations were done simultaneously in both groups of patients.

#### CONCLUSIONS

1. Sera from twenty-eight adults, eleven asthmatic and seventeen normal subjects, were analyzed for potassium.
2. Determinations one minute, ten minutes and thirty minutes after subcutaneous injection of epinephrine, failed to show any significant alteration over the pre-injection serum potassium level in normal and asthmatic subjects.
3. The serum from normal subjects showed no alteration in serum potassium level after subcutaneous injection of physiological saline, at one, ten, and thirty-minute intervals.
4. There was likewise no significant difference between the values for serum potassium obtained in normal adults after injection of epinephrine or physiological saline.
5. The fasting serum potassium levels in asthmatic patients were significantly higher than in the normal subjects.

Acknowledgment: The author wishes to thank Dr. G. S. Eadie for the statistical analyses; also Susan S. Butler and Sarah W. Levy for technical assistance.

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USE OF SYNTHETIC DIET FOR FOOD ALLERGY AND TYPHOID. Olmsted, W. H., Harfond, C. G. and Hampton, S. F.: *Arch. Int. Med.*, 73:341, (April) 1944.

A diet composed of nutritional factors in chemically pure form is described for use in food allergy, typhoid and in differentiating food allergy from other GI complaints. Amino-acid mixtures supply the protein requirements, dextrose is the best source of carbohydrate, and the oils of cottonseed, corn and olive are available for the fat content. Salt mixtures and vitamins in pure form, round out this synthetic diet. The mixture of these substances may be made up in any desired volume and the caloric intake may be varied by feeding more or less of the suggested sample preparation: 70 grams amino acid, 140 grams of oil and 250 grams dextrose and 20 grams salt mixture. Vitamins are given separately. Since the taste of the feeding is unpleasant, a Levine tube is used for feedings at two to four hour intervals.

Nine brief cases of suspected food allergy are described and the results of the use of the synthetic diet are indicated and tabulated. In those cases where food was a definite cause of the symptoms, marked improvement was obtained. The diet has almost no residue. This synthetic diet can be given successfully and satisfactorily to typhoid patients in that it supplies adequate nutritional factors with a minimum of residue.

L.J.H.

# ROUTINE TECHNIQUE OF ADMINISTRATION OF ANTIGENIC SUBSTANCES TO HYPERSENSITIVE PATIENTS

## A Suggestion for Modification

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San Francisco, California

ALL textbooks on allergy contain instructions for the administration of antigenic substances to patients who are found to be sensitive on testing by the scratch method or the ophthalmic test, or whose sensitivity was revealed by systemic or constitutional reactions after injections of an unsuspectedly antigenic substance. I am referring especially to patients who are hypersensitive due to previous injection of the antigenic material. The following discussion does not apply to primarily sensitive patients, usually called atopic, such as patients with a history of sensitivity (asthma, urticaria, et cetera) to horse serum and dander; in these patients administration of the antigenic material seems entirely contra-indicated on account of the danger of fatal allergic shock, and every effort should be made to avoid such injections.

The usual instructions are based on desensitization of the patient by small increasing doses of the antigenic substance. The method is quite satisfactory, as ample experience demonstrates. The instructions include the advice to have adrenalin ready to combat undue reactions of hypersensitivity. I believe it is theoretically sounder and practically easier and safer to carry out the desensitization and the administration of the antigenic substance with the patient under the influence of a comparatively large dose and the sustained effect of adrenalin. For that purpose, I recommend the administration of one c.c. adrenalin in oil twenty minutes prior to the administration of the final dose of antigen. The least this technique will do is to minimize a general reaction. The most it may do is to prevent it entirely. Of course, it does not safeguard against the delayed type of shock; the patient will have to be watched for a suitable period of time.

This method is especially valuable for the administration of hormonal extracts to moderately and mildly hypersensitive patients in whom such injections are necessary for various reasons, such as: the administration of insulin in hypersensitive patients where acidosis or coma makes the desensitization, at the time, impossible or impractical; the administration of liver extracts in severe stages of pernicious anemia; the administration of hormonal substances which are inefficient or ineffective by oral administration such as extracts of anterior or posterior pituitary extracts, or androgens, estrogens or parathyroid hormones, or substances like diodrast.

This simple modification has proved a valuable addition to the technique of administration of antigenic substances to hypersensitive patients.

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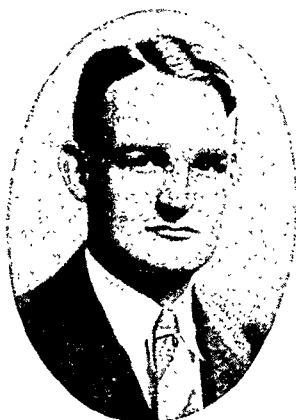
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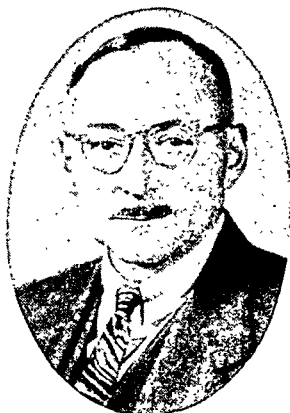
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# Editorial

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## RESEARCH IN ALLERGIC DISEASE

Research in our special field is and must always be one of the most lively interests of the College. Yet we must confess our recognition of the limitations impeding organized attempts to implement this urgent interest.

The human creative spirit is an individual quality that functions best not in group effort but in solitude; the new ideas that are the stepping stones of cultural progress are usually born in a spiritual loneliness.

Although the formulation and the preliminary testing of an idea are originally activities of a single individual, the development of the idea for practical application requires, from the beginning, the co-operation of many others who, in turn, however, make their essential contributions, also individually. The relative value of these "developmental" researches is often difficult to assess. For example, the forgotten report of Roemer on the intracutaneous technique of determining small quantities of diphtheria toxin and antitoxin would have remained sterile but for Bela Schick; and had it not been for the great experiment of William H. Park in the control of diphtheria in New York City, as Schick himself remarked at the reception upon his arrival here from Vienna, there might never have been a Schick test. The test was "made" by Park's practical use of it.

Evidently, then, our endeavors to encourage scientific research in allergy must be directed to individuals, but we are sometimes none too sure that we are supporting the right project in the right way. We can only believe that any effort is likely to be better than none and hope that inscrutable chance may one day reward us.

In considering possible ways in which we might encourage profitable investigations, the rather hazardous notion came to mind of suggesting specific research-projects concerning a question of fundamental character.

The series of papers by Arthur F. Coca<sup>2</sup> on familial nonreaginic food allergy that we have published has not escaped the notice of our readers. It is a striking fact that notwithstanding the revolutionary nature of his reports, the meticulous documentation of all of his statements, and the personal interest that his findings must have for a large proportion of our readers, no attempt has been reported by a reputable allergist to refute or confirm his conclusions.

The only publications concerning this matter that have been made by others are those of Arthur Locke and his associates<sup>1</sup> and of A. Sumner Price<sup>3</sup> (immunologist and pathologist, respectively), and we should point out that the conclusions of both of these reports are wholly in agreement with those of Coca.

## EDITORIAL

Whatever our first impression may have been about this thesis, we believe it to be wrong to allow skepticism to prevent us from exploring the matter without prejudice.

We suggest, then, the following projects :

1. The application of the statistical method in an inquiry as to the non-reaginic allergic nature of "infectious asthma," chronic rhinitis, epilepsy, hypertension, gastric ulcer, and others of the list of symptoms to be found in Coca's monograph (Charles C. Thomas, publisher).

2. The first condition for such an enterprise is obviously mastery of the author's diagnostic method. This is at least a half-time job, probably of long duration, to be undertaken only by a wholly unprejudiced man or woman who has already adequate experience in allergy and also in the scientific method.

The statistical method discussed in this monograph is relatively uncomplicated, and a series of 100 or more cases, with an equal number of unselected controls, should provide sufficient data for acceptable conclusions.

3. The editors are interested to receive, at least for our information, detailed reports of cases that have been treated with this method. The entire pulse-diet record would be essential to an evaluation of the procedure.

If a sufficient number of satisfactorily completed case records should be received from several observers, we might see our way to prepare a joint publication of them.

We also offer our aid in enlisting Dr. Coca's suggestions to anyone who wishes to undertake one of the above-mentioned research projects.

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## ADRENALIN AND RELATED SUBSTANCES IN BLOOD AND TISSUES.

Raab, W., *Biochem. J. Lond.*, 37:470, (Oct.) 1943.

The author states that results obtained with accepted methods for the determination of adrenalin in blood and tissues are not due to adrenalin itself. Adrenalin-like substances containing a catamol nucleus as well as ascorbic acid will produce similar results. Shaw's method (described) can be used, however, for adrenalin determination even though its specificity is not for this one substance. L.J.H.

# Progress in Allergy

## A REVIEW OF RECENT MISCELLANEOUS LITERATURE

MAJOR LAWRENCE J. HALPIN, MC, AUS

### *Miscellaneous*

*Army Allergy.* French, S. W., and Halpin, L. J.: *Ann. Allergy*, 1:1, 1943.

An allergy service, comprised of fifty-nine individual clinics, has been instituted in the Fourth Service Command, as of March, 1942. Preparation and standardization of pollen and other inhalent extracts have been completed at very low cost. All extracts are standardized on nitrogen content. Methods of investigation and therapy have been standardized so that each clinic is using the same method for recording reactions and instituting therapy. Tabulated reports from twenty-one clinics are presented. A total of 3,917 patients was seen in these clinics. These have been presented for discussion as follows: 1,269 patients with seasonal hay fever, 283 with seasonal bronchial asthma, 192 with seasonal hay fever complicated with bronchial asthma, 759 with perennial bronchial asthma, 770 with perennial allergic rhinitis, 350 with urticaria, 79 with migraine, 73 with gastro-intestinal allergy, 138 with eczema, 521 with food allergy.

Admission to allergy wards in hospitals was necessary in 1,153 instances. Of these, 820 (71 per cent) were asthmatic. An average of 18.1 hospital days was recorded for each patient. Only 195 patients seen on allergy service were eventually discharged from the Army because of the failure to respond to therapy; as compared to 267 that were reclassified to L. S. and maintained on duty.

*The Problem of Allergy at an Army Air Forces Hospital. 1. Respiratory Allergy.*

Hampton, Stanley F., and Rand, Harold: *J. Allergy*, 15:355, 1944.

Authors' summary:

1. A report of the activity of the Allergy Section and Clinic, AAF Regional Hospital, San Antonio Aviation Cadet Center, San Antonio, Texas, from August 1, 1942, to August 1, 1943, has been presented.
2. Eight thousand four hundred and nine clinic visits were made by Air Forces personnel to the Allergy Clinic of this Hospital.
3. One thousand five hundred and forty-one new patients were examined by the Allergy Section of this hospital.
4. Nine hundred and twenty-one of the 1,238 cases of allergic diseases were respiratory allergy (hay fever, vasomotor rhinitis and bronchial asthma).
5. One hundred and six or 8.9 per cent of the 1,191 men receiving the Certificate of Disability for Discharge under Section 2, AR 615-360 (Nov. 26, 1942) had allergic diseases. Eighty-six (7.48 per cent) had bronchial asthma.
6. Three and seven-tenths per cent of candidates for aviation training who were disqualified because of failure to meet the physical requirements (AR 40-110, Dec. 3, 1942) had allergic disorders.
7. The factors used in determination of fitness for aviation training of individuals with or suspected of having respiratory allergic disease are discussed.
8. The greatest problem of allergy has been *intrinsic* bronchial asthma associated

Major Halpin's work on the above Review was interrupted, and therefore this Review is not written in narrative form as are those which have heretofore been presented in THE ANNALS. To the carefully prepared abstracts of Major Halpin have been added some abstracts of articles published subsequent to the time when he was obliged to discontinue the assignment.

Secretary, Editorial Board

## PROGRESS IN ALLERGY

with chronic respiratory infection. The high incidence of this syndrome in the young Air Forces age group is discussed.

*The Significance of Allergy in Military Medicine.* Gold, Edwin M., and Blazemore, James M.: J. Allergy, 15:279, 1944.

This is a report of the incidence of allergic diseases in a large Station Hospital and a method of pre-induction evaluation of the allergic state. Composite statistics are presented from January 1, 1942, to December 31, 1942. The disposition of all allergic patients is summarized. The length of service in the Army prior to the time of the patient's disability discharge is tabulated. It is shown that 65.9 per cent had less than six months' service prior to discharge, and 21.33 per cent had less than thirty days' service. Thus the importance of special allergy studies prior to induction on all patients with a history of allergy is emphasized. Criteria are presented when determining the disposition of soldiers as well as candidates for induction. The authors conclude that the universal use of pre-induction consultation service will eliminate needless waste of time and expense in initial training and subsequent disposition of the physically incapacitated soldier. They urge the adoption of standard detailed criteria when determining disposition of these patients and suggest a method of eliminating allergic inductees.

*Army Allergy, Fourth Service Command, 1943.* French, S. W., and Halpin, L. J.: Ann. Allergy, 2:365, 1944.

The authors reported on a total of 32,046 patients who had passed through sixty-seven allergy clinics in the Fourth Command for a period of one year. Included were 6,842 with poison ivy, 1,785 were civilian dependents of men in uniform, and the remaining 23,419 were military men. Eight thousand one hundred and thirty-nine patients were hospitalized on account of their allergies with a total of 172,455 days in the hospital. It is estimated that in this single Service Command the valuable services of 20,000 men were saved to the Army. There are now eighty-nine allergy clinics operating as parts of station hospitals in the Fourth Service Command alone. Medical men in charge of these stations are selected from a group specially trained in allergy procedures of testing and treating. The laboratory of the Command produces its own allergens and other materials for both diagnosis and therapy, supplying not only the eighty-nine clinics but many more in other Service Commands. Thus, uniformity of diagnostic and treatment procedures with standardized extracts on a vast scale makes for more accurate and uniform statistics.

*The Allergic Problem of the Inductee, the Soldier of the Veteran.* Shahon, Henry I.: Annals Allergy, 2:413, 1944.

1. The difficulties encountered by the examining physician of the Induction Board are discussed.

2. The important questions for the detection of the allergic manifestations in prospective soldiers are pointed out.

3. The allergic problem as encountered in the Army is briefly mentioned.

4. The benefits that honorably discharged veterans receive are amply discussed.

5. This question is still debatable, namely: How is the Rating Board specialist going to know whether the allergic disease existed prior to induction or enlistment? If at the time of such examination, the examiner finds that the physical examination is negative and that the history does not suggest the existence of allergy in the family, and the allergic tests if performed are negative, then it is safe to assume that the allergic disease or manifestation was not there at that time. If, later, this soldier develops any allergic disease, it can be said that it developed during service. Later, when this soldier is discharged from service, service con-

nection for such a disability can be given. It is true that allergic diseases are not directly inherited and the tendency alone is inherited, yet no one can foretell the exact time of their appearance in life. It is possible that factors like overexertion, worry, exposure to cold or excessive heat, dampness, emotional strain and many others might precipitate the appearance of that hereditary tendency.

If, on the other hand, the allergic disease was present at the time of induction or enlistment to a degree hardly noticeable, and later it became greatly manifested with symptoms so disabling as to cause separation from the service, it can be said with some degree of certainty that this disease undoubtedly was aggravated by service.

*Severe Urticarial Reaction Due to Pooled Human Plasma.* Dickstein, Bernard: Ann. Allergy, 2:327, 1944.

1. The severe reaction of the patient was an allergic one due to elements specifically present in Pool 109 plasma and that these elements were antigens from milk, beef and lamb.

2. That no allergic reaction to human plasma *per se* occurred.

3. The chance of such reactions will be less if (a) blood donors avoid all food for at least six hours before giving blood, and (b) as many donors as possible contribute to a pool in order to dilute such allergens as might be present in individual instances.

*Blood Studies in Allergy. I. The Direct Counting Chamber Determination of Eosinophils by Propylene Glycol Aqueous Stains.* Randolph, T. G.: J. Allergy, 15:89, 1944.

A white cell diluent of phloxine and methylene blue dissolved in equal parts of propylene glycol and water permits the counting chamber differentiation of eosinophils on the same specimen used in determining the total leukocyte count. This technique has numerous advantages in comparison with previously described methods of enumerating eosinophils and would appear to be more accurate than the indirect method now in general use.

*Blood Studies in Allergy. II. The Presence in Allergic Disease of Atypical Lymphocytes and Symptoms Suggesting the Recovery Phase of Infectious Mononucleosis.* Randolph, T. G., and Gibson, E. B.: Am. J. M. Sc., 207:638, 1944.

The authors noted the similarity between atypical lymphocytes in the peripheral blood of allergic patients and those cells seen in the recovery phase of infectious mononucleosis. Inasmuch as both allergic reactions and infectious mononucleosis may produce symptoms of weakness, fatigue and lassitude the differential diagnosis is often difficult. The findings and impressions gained from a study of twenty-four allergic patients who had clinical manifestations of allergy along with the complaint of fatigue are reported.

*Allergy in Relation to the Genito-Urinary Tract.* Warrick, J. Thomas: Ann. Allergy, 2:396, 1944.

Allergy definitely must be considered as a cause of genito-urinary symptoms when they cannot be attributed to other causes, when they can be produced at will by the inhalation or ingestion of proven allergens, and when they can be controlled by withdrawal of the allergens. These symptoms may include frequency, painful urination with burning, tenesmus, nocturia, enuresis, ureteral colic, dysmenorrhea, leukorrhea, vulvar and genital irritation, and uterine contractions to the extent of terminating a pregnancy.

The rarity of genito-urinary allergy is understood, and evidence should be carefully weighed before a definite diagnosis is made. The diagnosis is substantiated



by other frank allergies in the personal and family history, but it should be made only by exclusion and after therapeutic trial. The cases presented offer substantial evidence of genito-urinary allergy as the explanation of the symptomatology.

The possibility of an allergic reaction in the genito-urinary tract must be considered in the treatment of pregnant women. Reactions to serum or ragweed hypsensitization may cause abortions or premature labor.

Experimental work substantiating the fact that the tissues of the genito-urinary tract manifest a frank allergic or shock reaction is cited.

Close co-operation of the allergist and urologist is necessary if genito-urinary allergy is to be ruled out or, if proved, to be properly managed and results obtained.

*Carbon Dioxide by Inhalation as Expectorant.* Banyai and Cadden. JAMA, 123:1078 (Dec.) 1943.

Banyai and Cadden studied the clinical use of carbon dioxide inhalations in tuberculous patients. A mixture of 10 per cent carbon dioxide and 90 per cent oxygen administered by the closed method through a mask, or by the open method through a glass tube, is well tolerated. The relief obtained is noticed subjectively and objectively: spells of strenuous, exhausting coughing are prevented and thereby rest is secured for the patient and particularly for the lungs; an unproductive cough is transformed into a useful one; directly after inhalation the amount of expectorated sputum is increased and its character changed from a heavy, thick and tenacious type into a thinner, serous and more watery kind; the use of expectorant drugs and narcotics can be reduced.

The effectiveness of carbon dioxide is attributable to the facts that (1) it is a powerful respiratory stimulant and it induces increased inspiratory movements of the thorax, which in turn cause a stretching and dilatation of the bronchial tubes; (2) it stimulates the myoelastic structures of the lung and leads to a forceful peristaltic movement of the bronchi; (3) it liquefies mucopurulent inflammatory exudate that stagnates in the bronchial tract. The treatment is indicated whenever there is an accumulation and retention of inflammatory exudate in the bronchial tract and its evacuation, in spite of strenuous cough, is inadequate. The treatment should not be given to patients who have had recent pulmonary hemorrhage; to those with severe emphysema; when extensive pulmonary fibrosis is present without atelectasis, bronchiectasis or mucopurulent retention in the air passages; to patients with acute plastic pleurisy and pleurisy with effusion; to hypertensive patients, and when the cause of cough is outside the lungs.

*Hypersensitivity from Inhalation of Atomized Fluid Antigens.* Hopps, H. C., and Moulton, Stanley: JAMA, 123:1051, (Dec.) 1943.

Inhalations of finely atomized specific antiserum have been suggested for the prevention and treatment of influenza. A possible hazard of this experimental procedure has just been recorded by Hopps and Moulton. Their report is based on tests made with five antigens (nonhomologous) on guinea pigs and rabbits. The animals were placed in a closed chamber and exposed for twenty minutes to finely atomized particles of the various serums. By the third of the three weekly exposures many mild reactions were observed. By the fifth week of such treatment allergic reactions were severe. Several of the sensitized animals died in the chamber during exposure to the atomized specific antigen. Since serious allergic reactions and fatal anaphylactic shock have occurred in animals from a procedure which has been suggested for human beings, further human studies should be pursued with great caution. Routine use of aerosols of this nature is not now desirable.

*Instructions for Venipuncture and Intravenous Therapy.* Lundy, J. S., Adams, R. C., Seldon, T. H.: Proc. Staff Meetings Mayo Clinic: 19:152, (Mar. 22) 1944.

Standardization of intravenous equipment for institutions is advised. In the procedure of venipuncture, the use of local anesthetic is recommended so that patient may have painless management. If the vein is small, insert needle with bevel down; if large vein, bevel may be up. Failure to utilize many available veins (in hands) and failure to take measures (moist heat applications) which cause full vein distention are cited. Tourniquet about 1 to 1½ inches above site of venipuncture produces the best distention of veins in that region.

*Venipuncture in Presence of Edema.* Schwartz, Steven O.: J. Lab. & Clin. Med., 28:1629, 1943.

A method of easy venipuncture in presence of arm edema is described: Place the thumb over antecubital space and exert pressure for 30-60 seconds with pitting produced. Antecubital veins stand out in bottom of "pit" since fluid has been expressed from both overlying tissue and that of the surrounding veins.

*Use of a Nebulizer to Produce Oxygenated Vapor: Report of Case of Acute Laryngotracheobronchitis.* Albers, G. D.: Proc. Mayo Clinic Staff Meetings, 18:511, (Dec. 29) 1943.

Acute fulminating laryngotracheobronchitis in childhood demands early tracheotomy and the administration of adequate moisture and oxygen. This crust formation and toxemia can be abated. The author describes the use of a nebulizer containing water through which pure oxygen is passed. The nebulizer is attached to the tracheal tube and adjusted to permit an adequate flow of oxygenated vapor. Necessary parts may be assembled from available oxygen apparatus. Case report.

*Possible Etiology of Appendicitis.* Dutton, L. O.: Ann. Allergy, 1:17, 1943.

Certain abdominal complaints of allergic origin may simulate a surgical condition. Dutton presents a clinico-pathological concept of appendicitis which accepts allergy as a fundamental etiologic factor. Such a consideration clarifies many points for an otherwise confused etiological situation. 123 consecutive cases of appendicitis were studied with clinical diagnosis as follows: acute 77, subacute 19, chronic 27. The pathological diagnoses were varied and showed little correlation between symptoms and pathological findings.

Without mechanical factors, only edema can account for obstruction. Dutton believes this functional edema to be allergic, inasmuch as this edema, capillary congestion and eosinophilic infiltration are reversible and similar to allergic tissue response. Throughout this series of cases these features of allergic reaction were seen in various degrees. A history of allergy was obtained from 87 of these patients, of whom 45 had had hay fever, asthma or urticaria. The author's presentation pertains to allergic reactions leading to appendicitis; not to symptoms simulating appendicitis. He recommends continued practice of treating appendicitis as a surgical disease; even though the allergic considerations may be sound and valid.

*Observations on Bacterial Allergy in Scarlet Fever.* Conner, James A., and Milzer, Albert: Illinois M. J., 84:214, 1943.

The authors believe hemolytic streptococci may be implicated in the appearance of urticaria in patients convalescing from scarlet fever. There was elevated temperature associated with these skin lesions. Urticaria showed late occurrences in the disease (eight to twenty-six days). All three cases presented were those of uncomplicated scarlet fever. Patient one had two previous attacks of scarlet fever. There was urticaria with the second attack although the patient had received no convalescent serum. Positive skin tests were obtained with cultures from the throat.

## PROGRESS IN ALLERGY

Skin reactions are separate and distinct from Dick toxin results. One should consider the possibility of correlation of streptococcus allergy to delayed or late hemorrhagic nephritis and nonsuppurative arthritis. Most cases in the past were thought to be due to serum or food, or drug. Case reports.

*New Interpretations of the Allergy Cutaneous Test.* Stoesser, A. V.: J. Lancet, 64:145, 1944.

In a pediatric allergy clinic, the author found the puncture method of endermal testing to be productive of the best and most accurate results. It was determined that the multiple food reactions were of the greatest importance in eczema, with the reactions to dairy products being of particular significance. In allergic rhinitis, cereals, dairy products, and chocolate were most important. Meat, fish, or nuts deserved first consideration in the asthmatic child. Inhalant reactions increased in importance with the age of the patient to school age and puberty. Positive reactions to animal emanations, feathers and cottonseed were considered as of definite value regardless of the size of the reaction.

*New Technique for Cutaneous Testing.* Levinton, James: J. Allergy, 15:300, 1944.

In this preliminary report the author proposes a new method of skin testing. This is by means of an apparatus which consists of a dental drill, mounted on a small portable motor, similar to that used by engravers. This easily carried apparatus is used to peel the epidermic cells by means of slight friction when the allergic extract is applied to the rubbed areas in the usual manner.

*Syringe Control in Passive Transfer Reactions* Simon, Frank R.: Ann. Allergy, 2:15, 1944.

Perfect control of skin reactions has been afforded in passive transfers by the transfer control (testing site not previously sensitized with serum) and by specificity control (injecting extracting fluid into sensitized area). Simon adds "syringe control" to the above two. After thorough cleansing and sterilization, the syringe is partially filled with extracting fluid, which is brought into contact with all parts of the plunger and barrel of the syringe. Test sites of sensitized and nonsensitized skin are then injected with this fluid from this syringe. Equal and negative reactions then determine the acceptability of that syringe for further use with that particular serum.

*Vascular Allergy.* Harkavy, Joseph: J. Allergy, 14:507, 1943.

Sixteen cases of bronchial asthma have been observed since 1936. Four of these died and their necropsy reports are presented. All sixteen patients had chronic sinus infection which was regarded as a source of bacterial sensitization. Demonstrable reactions were noted on testing with staphylococcus, streptococcus and pneumococcus vaccine prepared from cultures of sputa and sinus washings. Food and pollen sensitivity were also responsible in seven of sixteen cases.

Clinically most all cases had similar histories and findings. Sterile pleural effusion had developed in eight cases, with eosinophilia 85 to 100 per cent in the fluid. Associated allergic manifestations varied from urticaria and purpura to polyarthritis and polyneuritis. Leukocytosis was present in most cases; marked eosinophilia in blood, bone marrow and serous fluids.

Detailed clinical, laboratory and necropsy reports were made of two male and two female deaths. Vascular lesions of particular import, characterized by marked eosinophilic infiltration, were found in the heart, lung and fibrous tissue. In one patient necrotic lesions in the liver and spleen were tuberculous to section, but no bacilli were found.

Characteristic perivascular lesions were present in the gastro-intestinal tract and kidney; the lesions in the latter organ entered the clinical picture in only one case

causing hypertension and uremia. These vascular reactions are important in this symptomatology as evidence of allergic patients responding in a hyperergic manner to antigenic excitants. In bacterial allergy, symptoms may show up not only with direct infection, but with lighting up of old site, with toxins or with viruses. Various stages of vascular involvements were seen in same patient and in same organ. Venous involvement occurred in only one case.

Perivascular eosinophilic infiltration, necrotizing arteritis and periarteritis nodosa are hyperergic, exudative stage (reversible), while endarteritis obliterans and vascular fibrosis are anergic (irreversible). Eosinophilia is noted inversely to the degree of anergy. Harkavy considers bronchial asthma to be an expression of a hyperergic vascular response and accompanying vessel changes not representative of disease entities, but rather qualitative and quantitative degrees of hyperergic and anergic reactions. The heart in bronchial asthma may be normal, hypertrophied or directly involved as part of the hyperergic vascular response. Early diagnosis, correct therapy, change of climate, et cetera, in this type of asthma may bring about reversibility of hyperergic responses.

*Lessened Sensitivity to Tuberculin in Acne.* Lynch, F. W.: Arch. Derm. & Syph., 49:174, 1944.

The author shows that of 13,748 students, 3,549 had positive reactions to the Mantoux test and 3,997 had acne. Over a three-year period, positive Mantoux tests were found more often in absence of acne than when acne was present. Data given suggest that there is lessened sensitivity to tuberculin in persons with acne.

*Canine Sensitivity to Ascaris Antigen.* Brunner, M., Altman, Irving, and Bowman, K.: J. Allergy, 15:2, 1944.

Dog and pig ascaris antigen was used for intradermal testing on 24 dogs. Positive cutaneous reactions were obtained in 50%. Constitutional reactions from skin testing were noted in two dogs, both of whom had had previous nematode infection. Evidence of skin sensitizing antibodies in the sera of these dogs was established with the appearance of positive passive transfer sites in four of five normal dogs and in six human subjects. The authors also present evidence of active sensitization with ascaris extract. These antibodies were heat labile, thus resembling human atopic reagins.

*Relation of the Dose of Antigen to the Degree of Anaphylactic Shock in Dogs.* Dragstedt, Carl A.: J. Immunol., 47:505, 1943. Abstracted in Ann. Allergy, 2:66, 1944.

*Hypersensitivity: A Neglected Phase of Allergy.* Bruck, Clifford F.: J. Mich. State Med. Soc., 42:10, 1943. Abstracted in Ann. Allergy, 2:345, 1944.

*Diagnosis of Hydatid Disease.* Bull. Lederle Lab., 11:29, 1943. Reviewed in Ann. Allergy, 2:185, 1944.

*Allergic Phenomena in Relation to Abdominal Wound Evisceration.* Henry, M. G.: Amer. Jour. of Surg., 54:118, 1944.

Allergic reactions must be considered in the question of evisceration etiology. It is admitted that generalized cachexia plays an important part in the production of wound separation; but evisceration does occur in normal, healthy, individuals. In a case reported, no semblance of chromic gut remained in the abdominal wound that had eviscerated on the fifth day post operation. This same patient had had complete healing of a thyroidectomy wound six months previously; at which operation no chromic gut was used. Had the suture material been defective, total and complete absorption would not have occurred in this short time. Twelve addi-

tional cases were cited as further illustrations. The author suggests that a specific individual may be sensitive to the chromic gut used as suture material. These patients usually ail continuously from the time of the operation to the day of evisceration. There are present a low grade temperature, elevated pulse, distention, gas pains, and progressive ileus. The author believes there is some allergic substance produced in the wound which acts as a toxin to the patient, and dissolves the catgut more rapidly than normal, and which prevents normal healing. The source of the gut (sheep) is mentioned in the allergenic consideration.

A sample of chromic catgut was taken up into 1/10 N sodium hydroxide solution and used as a testing material on a series of patients. Negative reactions were seen in all of these except in the original case reported. Discussion is presented of the surgical considerations given to patients who have had evisceration.

*Wound Disruption and Catgut Allergy: An experimental and clinical study, with a review of the literature.* Pickrell, K. L., and Clay, R. C.: *Surgery*, 15:333, 1944.

The general and local factors are considered by the authors as of importance in wound healing. Of the former, malignancy, hypoproteinemia, vitamin C deficiency, age of the patient, and presence of debilitating diseases are briefly discussed. Local factors considered are debridement, method of placing sutures, presence of infection, the type of surgery, drainage, tension and strain on sutures, and the size and type of suture material. It has been stated that a patient may be sensitized to catgut by previous operations, by previous protein therapy or by previous treatment with sheep's serum. Sixty rabbits and eighty guinea pigs were used in the present experiments. Sensitization was attempted by various means, with both plain and chromic catgut. Negative results were obtained here, as well as negative skin test reaction with catgut extracts. Tests for anaphylaxis properties were negative in various experiments. Disruptions occur regardless of the type (catgut, silk or wire) of suture material used. Review of the literature with bibliography.

*Tropical Eosinophilia.* Kendall Emerson, Jr. *U. S. Naval Medical Bulletin*, 42: 118, 1944. Abstracted in *Ann. Allergy*, 2:341, 1944.

*Relation of Spore Dimensions to Their Rate of Fall.* McCubbin, W. A.: *Phytopath.*, 34:230, 1944.

Starting with the observed rates of fall recorded for 2-fungus spores, formulas are derived which may be used to calculate with a fair degree of accuracy the probable rate of fall of spores of several typical shapes and sizes, if the ordinary spore dimensions are known. For round or oval spores the product of the length and width in "u" divided by forty gives the approximate falling rate in mm. per second. (From Biological Abstracts).

*The Pollen Content of the Air in Rio de Janeiro, Brazil.* Greco, J. B., and Lima, A. O.: *J. Allergy*, 15:138, 1944.

Daily pollen counts were made in five sections of the city. Slides were coated with glycerine jelly and methyl green. There is only one pollen season in Rio; this lasts from the middle of May to the middle of June. Only one type of pollen is found existent—grass. *Melinis minutiflora* is chief source of the grass pollen. Average counts reached the peak of approximately 58 pollen grains per 1.8 sq. cm. at the end of May in 1941; and the peak of 40 in early June, 1943.

*Pollen Studies in the Phoenix Area.* Randolph, H., and McNeil, M.: *J. Allergy*, 15:125, 1944.

The climate in this area has a low humidity and lack of rainfall. Pollen counts are much lower than in the Middle West. Total count seldom was over 30 per cubic

yard. Slides were coated with mineral oil or glycerine and exposed on a weather vane arrangement. Usual area covered is 1.8 sq. cm., representing one cubic yard of air. Authors recognize six families as the most frequent causes of hay fever: Graminae (grass), Compositae (composites), Amaranthaceae (amaranths), Chenopodiaceae (chenopods or goosefoots), Polygonaceae (buckwheat family) and Plantaginaceae (plantain family).

Pollen season begins in early February with cottonwood (2 weeks) and ash (6 weeks). Bermuda grass was noted in April and continued through the summer with a second rise in September. Rabbit bush (similar to ragweed) is important and begins in April and May. Beet-sugar pollen is important for those in the immediate vicinity. Carelessweed is important in August to November. Common ragweed is not found in the Phoenix area, and false ragweed is not numerous, but should be considered in October. Graphic pollen charts for 1934, 1935, and 1936 are presented.

*A Note on a Possible Allergic Factor in Altitude Sickness.* Baker, Julia: J. Lab. & Clin. Med., 29:831, 1944.

The author presents evidence to indicate the more common occurrence of allergic diseases at a higher altitude (Mexico City, 7,328 feet) than at lower ones. Case histories and data on 500 consecutive patients fifteen years of age and under have been reviewed in support of this contention. Of the 500 patients, 167 had severe hives or eczema. 100 of the 500 patients had diarrhea proven to be upon an allergic basis. Several typical instances are described. Baker feels that the anoxia of the high altitude may result in greater absorption and accumulation of protein products than at lower levels. Similar features are offered as an explanation of mountain sickness. Recommendations are made regarding avoidance of common offenders (egg, milk, wheat, etc.) and particularly the practice of overloading on any one food.

*Weather and Death in Asthma.* Petersen, W. F., and Vaughan, W. T.: J. Allergy, 15:97, 1944.

Several brief case histories and clinical pictures of fatal asthma are presented. All have been graphically (and in discussion) compared with temperature curves, the barometric pressure and the precipitation. In these cases, it is well demonstrated that the weather change preceding an asthmatic attack is usually that of falling temperature and that exitus occurs with subsequent rise of temperature. *Marked weather changes* and the body's physiological adjustment thereto are the important factors. If the combination of allergen, exposure, fatigue, infection, constipation, etc., is favorable to the development of an attack, the weather changes may become the determining factor. Other factors can initiate or accentuate the pendulation from one extreme state to the other. Among these factors besides weather are emotion, infection, physical activity, digestive function, endocrine (menstruation) and others.

*Plasma Treatment of Severe, Near-fatal Anaphylactic Shock.* Raynolds, Arthur H.: J. Allergy, 14:495, 1943.

Case report of reaction from pollen therapy. Diffuse swelling of arms, legs and face. Blood pressure 50 systolic with no diastolic heard. Epinephrine total 1.75 c.c. given in two hours. Weakness, nausea and itching persisted. Because of continued low blood pressure patient was given about 500 c.c. plasma. Discontinued because of chills. Blood pressure 96/60. Recovery. The author states intravenous plasma should be given early and in adequate amounts when there is excessive blood volume loss.

*Successful Treatment of Extreme Allergy to Bee Body and Bee Venom.* McLane, E. G.: Minnesota Med., 26:1061, 1943.

McLane reports a case in which marked sensitivity to bee body and bee venom was overcome with graduated injections of whole bee extract, followed by carefully

spaced bee stings. Inasmuch as this extract protected the patient from both bee emanations and stings, the author suggests that there is likely a common substance present in both allergenic sources. Bibliography.

*Brucella Allergy in Veterinarian.* Huddleson, I. F.: M.S.C. Vet., 4:10, 1943-44.

It has been observed that the percentage of positive reactions to Brucella antigen in noninfected (symptom free) persons has a direct relationship to the opportunity for exposure to infected animals or materials. From what is known of veterinary practitioners, it can be predicted that 90 per cent of veterinarians who work with infected animals will become sensitive within two years if proper precautions are not taken. Sensitivity increases on repeated contacts. Rubber gloves and sleeves when working with Brucella infection are recommended as protection. Those exposed can prevent passage of most of allergen through unprotected skin by rubbing bovine blood serum having high Brucella agglutination titer (1-5000 or above) over that portion of skin in contact with infective material. The serum precipitates the antigen and delays or prevents absorption.

*Philosophy of Scientific Investigation.* Preface to De l'anaphylaxie a l'immunité. Arthus, M. (Translated by Sigerist, H.): Bull. Hist. M. 14:373, 1943.

The difference between fact and its signification is capital. Fact has an absolute value while the value of its signification is only relative. The fact is accepted by all, but the signification may vary with different scientists. The rigidity of fact can be contrasted with the plasticity of its interpretation: "It is good to find the different veins in a mine, but it is better to explore one thoroughly; the others constitute reserves for the future." In this preface to his book, the ardent experimentalist warns the reader to beware of theoreticians and theories. Preservation of independence and originality in scientific investigation is all important for success.

*Importance of Dosage in Intradermal Immunization Against Transplantable Neoplasms.* Gross, L.: Cancer Research, 3:770, 1943.

One hundred ninety-five mice were injected intradermally with 0.02 c.c. of sarcoma cell suspensions which varied in concentrations from 0.1 to 20 per cent. The minimum tumor dose capable of producing sarcoma was determined at 0.02 c.c. of 0.5 per cent strength suspension. Accurate dosage is of the utmost importance in tumor immunity, since acquired resistance can be overwhelmed with massive dosages.

*Reactions to Parenteral Fluid Administration.* Strumia, M. M., McGraw, J. J., Jr., and Blake, A.: Ann. Int. Med., 19:718, 1943.

Various causes for reaction are discussed. Classification includes: (1) Causative agents inherent in fluid alone (pyrogenic, nitritoid, embolic and mechanical). (2) Inherent qualities of fluid combined with condition of patient. Included here are hemolytic and allergic. The latter reactions are attributed to substances of alimentary origin contained in whole blood, plasma or serum to which the recipient is sensitive. Localized urticaria usually present, but may be generalized with angio-neurotic edema and rise in temperature. Asthma is occasionally seen. Edema of the glottis must be considered. This occurs in 0.3-1 per cent of the transfusions. One should insist that the donor be fasting. Patients respond well to epinephrine. True anaphylactic reactions are rare. (3) Conditions which are inherent in the recipient alone (hyperhemolysis, liver disease, hypoproteinemia, cardiac insufficiency). (4) Those due to temperature, air emboli, free hemoglobin, et cetera.

*Biological Methods of Determining the Insecticidal Values of Pyrethrum Preparations (particularly extracts in heavy oils).* Tattersfield, F., and Potter, C.: Ann. Appl. Biol., London, 30:259, 1943.

Insects are killed by being hit with particles of insecticide and/or by contact

with a film of insecticide left on exposed surfaces. Evenness of the deposit is an important factor with oil media in the spray, because the medium itself is somewhat toxic. The same is true of the film technique, but it is more marked. The insect chosen for these tests was *Tribolium Castaneum* Hbst. The experiments were controlled as to dosage, insect, spray and film technique. Increasing the concentration was found to be more effective than increasing the deposit. No evidence was determined that the spray technique was better than the film exposure.

*Vernal Conjunctivitis (Spring or Vernal Catarrh).* Marton, Samuel: *Ann. Allergy*, 1:39, 1943.

The term is not satisfactory because the condition is not confined to spring, nor is the exudate catarrhal in nature. Clinically characterized by seasonal recurrence with symptoms confined to tarsal or limbal portions of conjunctiva. Acute stage characterized by redness, itching, lacrimation and mucoid discharge. The chronic form shows large papules on tarsal conjunctiva and the discharge changes to the lardaceous type. Chronic often confused with trachoma. The differentiating point is the history. If the onset is in the pollen season, with aggravation of symptoms during succeeding seasons, and with negative tests, a diagnosis of vernal catarrh must be made. Marton presents four cases of vernal catarrh in support of pollen as a prime etiologic factor. In treating the pollen dosages must be carried in high concentration.

*Adrenalin and Related Substances in Blood and Tissues.* Raab, W.: *Biochem. J.* London, 37:470, 1943.

The author states that results obtained with accepted methods for the determination of adrenalin in blood and tissues are not due to adrenalin itself. Adrenalin-like substances containing a catechol nucleus as well as ascorbic acid will produce similar results. Shaw's method (described) can be used, however, for adrenalin determination even though its specificity is not for this one substance.

*An Association Between Red-Green Color Blindness and Some Cases of Asthma and Hay Fever.* Molholm, H. B.: *J. Allergy*, 15:120, 1944.

Asthma and hay fever having onset before the tenth year shows a 2:1 majority for boys, suggesting transmission by sex-linked recessive factor. No difference in onset after tenth year. Red-green color blindness is definitely dependent, in all instances, on a sex-linked recessive factor. Of 357 male asthma and hay fever patients, 30 (8.4 per cent) were red-green color blind. This is about twice as great as for unselected males. Red-green color blindness was highest in those asthmatics without symptoms before 13 years. Similar, though not as marked, findings in the patients with hay fever. Only two red-green color blind persons were in a group of 67 with asthma appearing after 13th year. Indications are that hay fever in boys probably depends on a sex-linked recessive factor.

*The Alaskan Species of Puccinella.* Swallen, J. R.: *Washington Acad. Sci.*, 34:16, 1944.

*Puccinella* is a circumpolar genus of grasses well represented in Alaska. 13 spp. are described with key. The following new spp. are published: *P. grandis*, *P. borealis*, *P. globra*, *P. triflora*, *P. andersoni*, and *P. hulteni*. (From *Biological Abstracts*.)

*Pernicious Vomiting of Pregnancy due to Sensitivity to Semen.* James, D. W., and Wagoner, C. P.: *Int. Corres. Club Allergy*, 7:70, 1944.

The authors report a case of nausea and vomiting of pregnancy which is felt to be due to semen sensitivity. The use of a condom prevented subsequent episodes. The psychic factor was apparently ruled out in that the patient had possibility of



semen sensitivity explained to her and on one occasion she was unaware of semen exposure. Passive transfer areas were positive on testing.

*An Aid in Eliminating Dull Needles.* Lundy, J. S., Adams, R. C., and Seldon, T. H.: Proc. Staff Meetings Mayo Clinic, 18:417, 1943.

A magnifying glass mounted on a ring stand permits the easy inspection of sterile needles in order that their sharpness may be determined without fear of contamination.

*Allergy.* Hughes, R. F.: Canad. J. M. Tech., 5:174, 1943.

In discussing general therapeutic considerations, the author mentions methods other than skin testing that can be used in instances of food allergy. These are chiefly elimination diets, leucopenic indices, pulse acceleration test, and food diaries. Hyposensitization to inhalent allergens has been successful. Oral desensitization to foods is recommended. Drug therapy in allergy is designed to stimulate the sympathetic system, since the effects of allergy are those of parasympathetic stimulation. Epinephrine is most suitable.

*Periarteritis Nodosa; Report of Case.* Lichtman, A. L., Stickney, J. M., and Kernohan, J. W. Proc. Staff Meetings Mayo Clinic, 18:500, 1943.

Illustrative case report. Histogenetically, there is necrosis of the media with resulting extension of the inflammatory reaction and repair into perivascular tissues. Subsequent infarction produces disability. Marked variation of vascular involvement is outstanding characteristic. Occlusion of vasa nervosum has been a constant observation of authors. Eosinophiles are usually present in the inflammatory reaction. Symptoms vary with the degree of involvement of different organs and tissues, depending on interruption of blood supply. Asthma (in 15 to 20 per cent), eosinophilia (often 70 to 80 per cent) and peripheral nerve involvement are common characteristics of periarteritis nodosa. The etiology is probably allergic or infectious with neither definitely proven.

*Precipitation of Pulmonary Edema by an Overdose of Antigen in a Patient with Rheumatic Mitral Disease.* Deissler, Karl J.: Ann. Allergy, 2:299, 1944.

Cardiac decompensation occurred in a patient with rheumatic mitral disease as a result of an overdose of pollen antigen. The mechanism of this occurrence and the therapeutic implications are discussed.

It appears that this occurrence represents a special form of cardiovascular complication of a generalized reaction to an overdose of antigen in a cardiac patient.

It is believed that this type of response should be distinguished from both the systemic and constitutional types of reaction both on account of the underlying mechanism and the therapeutic implications.

*Immunity to Tetanus Induced by a Third Dose of Toxoid Three Years after Basic Immunization; Based on a Study of 38 Allergic Children.* Peshkin, M. M.: Am. J. Dis. Child., 67:22, 1944.

Thirty-eight allergic children were given a "booster" dose of 0.5 c.c. combined alum-precipitated diphtheria and tetanus toxoid. This was done three years after their basic immunization. Mild reactions were noted in 33 per cent of the children. One systemic reaction occurred in a child given the combined toxoids. An average of two months after the "booster" dose, scratch-test reactions with these toxoids were negative. Adequate tetanus antitoxin titers were noted within one month in all cases. This titer was higher and more prolonged than that following the basic immunization. The author recommends the use of alum-precipitated tetanus toxoid alone for this "booster" dose in order to keep local and systemic allergic reactions at a minimum level.

(Continued on Page 90)

# News Items

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Dr. Maurice S. Fox announces the opening of an office for the diagnosis and treatment of allergic diseases at 223 American Bank Building, Vincennes, Indiana.

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Dr. Lewis Palay, of Miami Beach, Florida, announces the opening of his office in the Medical Building, 541 Lincoln Road. His practice is limited to allergy.

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Dr. Theron G. Randolph, formerly in charge of the Allergy Clinic at the University of Michigan Medical School, has accepted a part-time research position in allergic diseases at Northwestern University Medical School and has started the private practice of allergy in Chicago, at 700 North Michigan Avenue.

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The contribution of Mr. Samuel Dorman, Long Beach, New York, to the Research Fund of the College, is gratefully acknowledged. Through Mr. Dorman, several other contributions to the Research Fund have been received, which were announced in the November-December, 1944, issue of the ANNALS OF ALLERGY.

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Lt. Col. Boen Swinny, of San Antonio, Texas, who has been serving in the Armed Forces for four years, has been Commanding Officer of the U. S. A. Hospital Ship for about a year. Doctor Swinny's office has been functioning under the direction of Dr. Pearl Zink during his absence.

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At the Seventh Annual Forum on Allergy, held at Pittsburgh, January 20 and 21, Dr. Mary Loveless of New York City was awarded first prize for the most meritorious work in the field of allergy appearing in the literature in 1944. Dr. Charles F. Code, Professor of Clinical Physiology, Mayo Foundation Graduate School of Medicine, Rochester, Minnesota, was awarded second prize. These prizes were made available through the Marcelle Award.

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The fifth semi-annual refresher course in laryngology, rhinology and otology will be conducted by the University of Illinois, College of Medicine, at the College in Chicago, March 26 to 31, inclusive, 1945. While the course will be largely didactic, some clinical instruction will be included. This course is intended primarily for ear, nose and throat specialists. As the registration is limited to thirty, applications will be considered in the order in which they are received. The fee is \$50. When writing for application, please give details concerning school and year of graduation, and past training and experience. Address Dr. A. R. Hollender, Chairman, Refresher Course Committee, Department of Otolaryngology, University of Illinois, College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

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## 1945 ANNUAL MEETING CANCELLED

The Board of Regents of the American College of Allergists, after consideration of all factors involved, officially announces the postponement of its second annual session, scheduled for Philadelphia, June 16 and 17. The action is taken this year voluntarily in order to co-operate to the fullest possible extent at the advice of the Office of Defense Transportation and in the interest of the nation's war effort.

A meeting of the Board of Regents will be held in June, at which time pertinent matters concerning the policies of the College to be instituted in 1945-1946 will be discussed and the various functions mapped out.

Plans are being made to hold an extensive instructional course in the fall at one of the Universities, and announcements concerning this will appear in the ANNALS OF ALLERGY.

# \* *In Memoriam* \*

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## DAVID R. GODLIN

Dr. David R. Godlin, of Miami Beach, Florida, died July 27, 1944, at the age of forty-three years, in New York City. He received his M.D. degree in 1926 from Columbia University College of Physicians and Surgeons and interned at Christ Hospital, Jersey City, New Jersey. He opened an office at North Bergen, New Jersey, where he practiced medicine until 1939. He was attending surgeon at Christ Hospital, a member of the staff of Margaret Hague Maternity Hospital, both of Jersey City, and a member of the Hudson County and New York State Medical Societies, as well as the American Medical Association. Doctor Godlin specialized in surgery in New Jersey and later in allergy, having taken advantage of various intensive courses in allergy at Postgraduate Hospital, New York City.

He became ill in 1939, having suffered a heart attack. He left his practice in New Jersey and moved to Miami Beach to regain his health and opened an office at 541 Lincoln Road. While there he began a mold and pollen survey of the state. He was on the staff of Jackson Memorial Hospital where he conducted an allergy clinic.

He is survived by his wife, Rose Godlin, and a six-year-old son.

Doctor Godlin won the respect and admiration of all who knew him. His keen interest in allergy and the progress he made in this field is evidence that the College has lost a valuable member.

FRED W. WITTICH

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## HARRY IKER

News of the death of Mr. Harry Iker, of Chicago, an Associate Fellow of the College, which occurred February 19, was received just as this issue of *THE ANNALS* was going to press. A fitting tribute to him will be contained in a forthcoming issue of *THE ANNALS*.

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## THE EFFECTS OF DIET ON THE EAR, NOSE AND THROAT. McLaurin, J. G., Dallas, M. J., 30:24 (Feb.) 1944.

Mucous membrane of the nose and throat serves as a guide to the type of food eaten in excess by the patient. In the age group ten to twenty, lymphoid tissue is present in proportion to the absence of fats from the diet; in twenty- to thirty-year-old groups, catarrhal discharge depends on a deficiency of leafy vegetables in food selection, and in older patients a granular pharyngitis is dependent on an excess of cereals and foods prepared with white flour. The author divides the color appearance of the nasal mucous membrane upon a red and a pale syndrome basis. The red septum syndrome is found in those patients with chronic tiredness, constipation, irritable temperament and no appetites. They have a low tolerance for acid-ash foods. The pale septum syndrome is found in the allergic patients. Itching of the nose, polyps, subnormal temperatures, low BMR and hypotension are usually found. These cases are dependent on an excessive intake of alkaline-ash foods. A blood count and hemoglobin determination are important as aids in correctly establishing these color changes which are due to three factors: capillary size, change in the volume of septal tissue cells and the amount of interstitial fluid. The patient with constant post-nasal drip usually is an excessive user of sweet foods. Correction and dietary therapy in each syndrome is the addition of alkaline-ash or acid-ash foods in each particular instance.

L.J.H.

# BOOK REVIEWS

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**A MANUAL OF SOIL FUNGI.** By Joseph C. Gilman, Botany Department, Iowa State College, 392 pages, 135 illustrations. Limited edition. Price \$5.00. Ames, Iowa: The Collegiate Press, Inc., 1945.

Contents: Key to the classes, orders and families of soil fungi: Phycomycetes, Ascomycetes, Fungi Imperfecti and Mycelia Sterilia. The entire text consists of a succinct, orderly and practical taxonomic description, supplemented with excellent drawings illustrating genera. The distinguishing characteristics of the various classes, orders, families, genera, species and subspecies of soil fungi are adequately described. There is an authoritative global listing of the countries and states where the various species are found.

The manual is a revision, with the incorporation of a great amount of additional material, of a manuscript entitled "A Summary of Soil Fungi" by the author and E. V. Abbott. Although written primarily for workers in the field of soil microbiology, there was such a demand for reprints of the manuscript by men in industry and in medicine that the new publication was made available.

The text is not an exhaustive study of the techniques required for an investigation of soil fungi, but "to be helpful in identifying molds already in cultures." In this, the author has been very successful.

Since certain common air molds, all formed in soil, are the cause of allergic diseases, allergists are now required to have a basic knowledge of molds not only for practical application but for further investigations of the relative importance of fungi, when causing symptoms of hypersensitiveness.

Since the development of the latter state as a result of extrinsic factors depends upon the amount of contact with any excitant indigenous to the environment of the allergic patient, the states and countries in which these fungi are formed furnish a valuable supplement to aerial surveys of fungi already made by those interested in mold allergy.

All allergists interested in molds in relation to their specialty should avail themselves of this valuable manual.

F.W.W.

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**HAYFEVER PLANTS.** Their Appearance, Distribution, Time of Flowering, and their Role in Hayfever, with Special Reference to North America. By Roger P. Wodehouse, Ph. D. (Lederle Laboratories). 245 pages. 73 illustrations. New and numerous tables. Series of Pl. Sci. Bks., vol. 15. Price \$4.75. Waltham, Mass.: Chronica Botanica Co., 1945.

This is an authoritative botany of hay fever by the author of "Pollen Grains," universally known by allergists. Contents: The Botany of Hay Fever; The Hay-fever Plants—Gymnosperms, Angiosperms, Monocotyledons, Dicotyledons; Regional Surveys; Glossary; Bibliography.

The first three chapters are devoted to pollens and pollination and the role that pollen plays in hay fever, as well as a description of all the plants known to cause hay fever, showing where they grow, when they flower and the characteristics which make them hay-fever plants. The last, or fourth chapter, is geographical, dealing with regional surveys with accurate and recent data on ten areas throughout the United States, besides Canada and Mexico. Numerous illustrations of plants and their pollen grains, mostly drawn by the author, are very informative and bring out details frequently lost by photography. There is a map of the ten hay-fever regions of the United States. The pollinating periods of hay-fever plants in these regions

represent accurate, recent surveys, with the most important plants clinically printed in heavy type. The print throughout makes it very easy reading, and the arrangement is excellent for ready reference. The references to local surveys of others are very complete, and there is a discussion on hay-fever resorts.

The book is indispensable to all physicians interested in allergy when managing their local hay-fever problems, and it is the most complete authoritative text on the subject today.

Medical allergists will welcome this authoritative book on the flora, responsible for clinical hay fever and asthma, indigenous to their respective areas, when treating their pollen-sensitive patients.

F.W.W.

### Proteins in Soy Milk Approximate Utilization of Egg Protein

Investigations recently conducted at Wayne University in Detroit have shown the soy proteins in Mull-Soy to have an average true digestibility of 89.6 per cent and an average biological value for maintenance of 95.6 per cent, compared with egg protein as 100 per cent.

The findings of this study using adult human subjects were published in a recent issue of the *Journal of Nutrition*, 28:209, 1944. The method of Murlin and associates was used to determine biological values.

Mull-Soy, a product of The Prescription Products Division of the Borden Company, has been used extensively for infant feeding, and also for children and adults, as a palatable, well-tolerated and easy-to-digest milk substitute.

### PROGRESS IN ALLERGY

(Continued from Page 86)

*Human Plasma and Serum Toxicity.* State, David, and Levine, Milton: J. Lab. & Clin. Med., 28:1786, 1943. Reviewed in Ann. Allergy, 2:66, 1944.

*Palindromic Rheumatism.* Hench, P. S., and Rosenberg, E. F.: Arch. Int. Med., 73:293, 1944. Reviewed in Ann. Allergy, 2:456, 1944.

*On the Anaphylactic Nature of Rheumatic Pneumonitis.* Rich, A. R., and Gregory, J. E.: Bull. Johns Hopkins Hosp., 73:465, 1943.

By comparing the peculiar lesions of rheumatic pneumonitis with those of pneumonitis seen in sulfonamide hypersensitivity, the authors show them to be basically identical. Both types of pneumonitis demonstrate capillary damage characteristic of anaphylactic reactions. The authors present these findings, therefore, as further evidence that the lesions of acute rheumatic fever may be anaphylactic in origin.

*Allergic Reaction to Dried Human Plasma.* Colonnell, William J.: U. S. Naval Med. Bull., 41:1356, 1943.

Angioneurotic edema, asthma and urticaria occurring in a patient transfused with blood plasma after having had two previous whole blood transfusions from the same donor is reported. Urticaria occurred following the second transfusion. There was no family or personal history of allergy. After reaction, the patient was found to be ragweed-sensitive (three plus), also one plus to same activated plasma (Dil. 1-10) that was used in transfusion. The donor was ragweed-pollen-sensitive. Ragweed allergen in pooled human plasma was demonstrated by passive transfer on three controls.

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## THE AUTONOMIC NERVOUS SYSTEM IN RELATION TO ALLERGY

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THE common manifestations of allergy, such as hay fever, asthma and eczema, and diverse anaphylactic reactions probably are invariably associated with abnormal functional states of the autonomic nerves. The latter may be induced by the tissue reactions to the sensitizing agent in question, but not infrequently the modified functional status of the autonomic nerves is a factor in the etiology of allergic disease. The so-called "allergic state" probably does not exist in the presence of a normal functional status of the autonomic nerves.

### NATURE OF THE ALLERGIC STATE

The nature of the allergic state as yet is obscure. A hereditary factor undoubtedly exists in many cases. The observation of Landsteiner and Chase<sup>23</sup>, confirmed by Jacobs, Kelley and Sommers<sup>22</sup>, that a strain of guinea pigs which is resistant to a given allergen may be obtained by selective breeding strongly supports this point of view. The hereditary factor may be concerned with the capacity of the organisms to produce tissue antibodies, the permeability of the tissue elements, including the capillary endothelium, or the release of substances such as histamine and acetylcholine, all of which processes may be influenced through the autonomic nerves.

Emotional factors in the etiology of allergic disease have long been recognized. These factors have gained increasing recognition, during recent years, in the causation of various allergic disorders. As Gillespie<sup>14</sup> pointed out, an asthmatic attack may occur as the accumulation of an anxiety, the

expression of an emotional conflict, a protest against an unwelcome situation, a means of escape or as a conditioned response. Urticaria of emotional origin is not uncommon. Abramson<sup>1</sup> reported the case of a woman aged thirty-one who, while suffering from certain mental conflicts, developed giant hives after swimming in cold water. The application of ice to her arm also resulted in the development of an urticarial wheal. When later her mental conflicts were adjusted her sensitiveness to cold disappeared. Numerous cases in which allergic symptoms of other types have been precipitated by emotional disturbances have been reported.

The emotional factors in allergic disease emphasize the role of the central autonomic centers, particularly those located in the hypothalamus. In a review of the nature of eczema, Milian<sup>26</sup> advanced clinical data in support of the assumption that the itching associated with this disorder is of central origin and that the associated capillary dilatation, edema and secondary vesiculation are related to abnormal vasomotor function due to the low threshold susceptibility of these nerves to itching. Lortat-Jacob<sup>25</sup> also demonstrated definite association of the sympathetic nerves and pruritis, erythema and vesiculation in the background of contact allergy. He cited the case of a woman with more or less generalized eruption, caused by working with synthetic vanilla, which was aggravated by pilocarpine and relieved by atropine. The cutaneous lesions in this case obviously were related to reflex activity mediated through central autonomic centers.

The most spectacular of all allergic manifestations, protein anaphylaxis, undoubtedly represents the results of the antibody-allergen reactions of the tissue elements. Certain allergic manifestations, e.g., those of physical allergy, cannot be explained on the same basis. A combination of heat, cold or sunlight with body proteins which could produce a new protein is inconceivable. In either case the functional disturbances bear essentially the same relationship to the autonomic nerves. They involve primarily tonic changes in the musculature of the visceral organs, including the vascular system. Since the tonus of the visceral musculature is regulated through the autonomic nerves, deviations from the normal tonic level of the visceral organs imply deviations from the normal functional autonomic balance. The changes in smooth muscle tonus commonly associated with allergic disease, e.g., the heightened tonus of the bronchial musculature in bronchial asthma and the increased gastro-intestinal tonus and motility associated with various allergic diseases, indicate heightened parasympathetic activity. The decreased vascular tonus, particularly in the shock tissue, commonly associated with allergic reactions are of the same order, although the efferent innervation of most of the blood vessels is mediated solely through sympathetic nerves. The decreased vascular tonus may be explained in part on the basis of decreased activity of the adrenergic vasoconstrictor nerves and in part on the basis of increased activity of the cholinergic vasodilators. The increased secretory activity associated with allergic catarrhal inflammation of the nasal, pharyngeal and bronchial

mucous membranes, the gastro-intestinal mucosa and the conjunctivae also indicate exaggerated parasympathetic tonus. The vasodilatation of the mucous membranes, indicating corresponding activity of the cholinergic vasodilator fibers, results in increased permeability of the capillary bed, which facilitates the discharge of serous fluid, thus providing the substratum for increased secretory output of the glands. Increased capillary permeability due to vasodilator stimulation, in the absence of allergic disease, has been amply demonstrated. Activation of the glands in the mucous membranes is mediated mainly through the parasympathetic nerves. Some of the most characteristic manifestations of allergic disease, therefore, are causally related to heightened parasympathetic or cholinergic reactivity.

Hyperreactivity of the cholinergic autonomic nerves associated with anaphylactic reactions in animals, in the absence of a pre-existing autonomic imbalance, has been amply demonstrated. In experiments on cats reported by Heim<sup>16</sup>, the intravenous injection of a serum to which the animals had been sensitized three to five weeks previously resulted in a marked increase in parasympathetic tonus and reactivity of the parasympathetically innervated tissues.

The localization and the limitations of the shock tissue present intricate problems which probably will find their solution in a more complete understanding of the role of the cholinergic autonomic nerves in allergic reactions. The discharge of nerve impulses through the sympathetic nerves, particularly when they emanate from higher autonomic centers such as those located in the hypothalamus, is diffuse and influences the entire body. This mode of action is one of the most significant aspects of sympathetic function. The high efficiency of the sympathetic nerves in effecting adjustments to external and internal environmental factors can be explained most satisfactorily on this basis. Totally sympathectomized animals may continue to live without apparent functional deficiencies while they are not subjected to conditions of physiological stress but they are unable to effect adequate adjustments to changes in temperature or to maintain the environment of the tissue elements in a constant state. Homeostasis is mediated primarily through the sympathetic nerves. The discharge of impulses through the parasympathetic or other cholinergic nerves is less diffuse and may be limited to a single organ or body region. This undoubtedly provides the physiologic basis for the fact that allergic reactions, as observed clinically, commonly occur in localized tissues known as shock tissues. The cholinergic influence in these reactions is indicated by the fact that, regardless of which shock tissue is affected, adrenin affords relief. The general adrenergic reaction tends to counteract the effect of the local cholinergic stimulation, wherever the disturbance may be. The experimental observation that the blood of rabbits in anaphylactic shock contains relatively large quantities of acetylcholine, whereas that of normal control rabbits contains none, supports this point of view.



## AUTONOMIC IMBALANCE

If the assumption that allergic reactions are constantly associated with a shift in the autonomic functional balance in favor of the cholinergic nerves may be regarded as well founded, the means by which changes in the functional autonomic balance may be detected deserve careful consideration. Therapeutic measures designed to restore normal autonomic balance also deserve consideration in the treatment of allergic disease.

The original concepts of sympathicotonia and vagotonia formulated by Eppinger and Hess obviously require revision. In the light of our present knowledge of the humoral transmission of nerve impulses and the distribution of cholinergic and adrenergic fibers in both divisions of the autonomic nervous system, the concept of a clear-cut functional difference between the parasympathetic and the sympathetic nerves is untenable. On the basis of this knowledge and the results of a study involving measurements, over an extended period, of twenty physiological variables of which at least twelve are mediated at least in part through the autonomic nerves, in sixty-two children six to eleven years of age, and a factor analysis of these data, Wenger<sup>32</sup> has proposed the following restatement of the theory of Eppinger and Hess:

(a) "The differential chemical reactivity and the physiological antagonism of the adrenergic and cholinergic branches of the autonomic nervous system permit of a situation in which the action of one branch may predominate over that of the other. This predominance, or autonomic imbalance, may be phasic or chronic, and may obtain for either the adrenergic or the cholinergic system. (b) Autonomic imbalance, when measured in an unselected population, will be distributed continuously about a central tendency which shall be defined as autonomic balance."

## CRITERIA OF THE AUTONOMIC FUNCTIONAL STATE

A test of autonomic function can be significant only if it indicates clearly whether an observed reaction is due to increased or decreased activity of either the adrenergic or cholinergic nerves. Tests which merely indicate a functional imbalance are of little value and may even be misleading, since they do not define the reaction in question in the neural and neurohumoral systems.

Circumvention of the difficulties in interpreting observed autonomic reactions in terms of neurohumoral processes has been attempted in various ways: (1) by recording the reactions of mechanisms which are innervated through only one division of the autonomic system, e.g., the nictitating membrane; (2) by elimination of either the sympathetic or the parasympathetic innervation of the organ in question; (3) by assaying *in vivo* or *in vitro* the neurohumoral mediator liberated; (4) by recording the action potentials of the respective autonomic nerves; (5) by analysis of the reactions to appropriate pharmacologic agents. All of these methods have been found useful but the interpretation of the results obtained is beset

with difficulties due to the tendency of autonomic reactions to bring about adaptive changes and to maintain the constancy of the internal milieu.

The tests which probably will be found most useful in the study of autonomic functional changes associated with allergic disease are those which involve reactions to pharmacologic agents. In general, individuals with exaggerated sympathetic tonus react more strongly to sympathomimetic agents than those with normal autonomic balance. Individuals with exaggerated parasympathetic tonus likewise react more strongly to parasympathomimetic agents than those with normal balance. The effect of a given dose of a drug like ergotamine, which tends to block the sympathetic or adrenergic nerves, or atropine, which tends to block the parasympathetic or cholinergic nerves, therefore, varies according to the functional balance of the autonomic system. In the presence of exaggerated sympathetic tonus a larger dose of ergotamine is required to block adrenergic function than in the presence of normal autonomic balance. Likewise, in the presence of exaggerated parasympathetic tonus a larger dose of atropine is required to block cholinergic function than in the presence of normal autonomic balance.

The assumption that ergotamine merely tends to block adrenergic conduction is misleading. Its primary action on smooth muscle, particularly that which is cholinergically activated, like the gastrointestinal muscle, is to cause contraction.<sup>30</sup> In the intact animal it increases intestinal motility, causes extreme miosis<sup>8,7</sup>, lowers blood sugar<sup>31</sup> and decreases blood pressure.<sup>33</sup> In certain cases the administration of this drug may be followed by increased blood pressure probably due to the contraction of muscular organs. Desensitization of the carotid sinus by ergotamine<sup>18</sup> may be a contributing factor in the rise in blood pressure in these cases. Ergotamine blocks the inhibitory effect of adrenin or sympathetic stimulation on cholinergically activated mechanisms. The inability of adrenin or sympathetic stimulation to block the spontaneous activity or relax the tonus of intestinal muscle in the presence of ergotamine can be explained most satisfactorily on this basis.<sup>9</sup> In the human placenta, which is devoid of nerves but rich in choline<sup>6</sup>, constriction of the blood vessels by adrenin is blocked by ergotoxine.<sup>10</sup> Cholinergic vasodilatation probably is normally inhibited by adrenergic sympathetic stimulation or inhibitory adrenin, resulting in constriction which is synergic with adrenergic constrictor activity. This inhibition of the vasodilators does not take place following the administration of ergotoxine; consequently, the rise is less marked or there may be an actual fall in blood pressure. A similar vasomotor reversal after eserine, which is abolished by atropine, has been demonstrated.<sup>5,17</sup> This also suggests that the inhibitory effects of adrenergic stimulation may be blocked in the presence of sufficient acetylcholine. Linegar et al.<sup>24</sup> have shown that the depressor effect of acetylcholine may be potentiated by ergotamine and that this action may be reversed by atropine. The chief value of ergotamine as an indicator of autonomic function undoubtedly lies in its effec-

tiveness in testing for the presence of sympathetic inhibitory and adrenin inhibitory effects on cholinergic functions.

The use of atropine to determine the role of cholinergic mechanisms in a given response has become almost routine in physiological experiments. The measurements sought by its use have been mainly of two types: (1) an index of the normal cholinergic activity as indicated by the changes induced when that activity is blocked, and (2) an index of sympathetic function as indicated by the total residual activity following blocking of the cholinergic transmission of nerve impulses in the sympathetic ganglia, the adrenal medulla and the central nervous system. The possible compensatory action of the carotid sinus and other moderator nerves may vitiate both these effects to some extent.<sup>9</sup> Atropine has nevertheless been found useful in the study of autonomic functions, particularly in psychopathic patients<sup>11</sup>, and synergic and antagonistic pharmacologic responses in normal and diseased human subjects.<sup>15,28</sup>

#### SIGNIFICANCE OF RESTORATION OF AUTONOMIC FUNCTIONAL BALANCE IN TREATMENT OF ALLERGIC DISEASE

The common association of allergic disease with functional imbalance of the adrenergic and cholinergic autonomic nerves and the evidence that hyperreactivity of the cholinergic nerves is a factor in the etiology of the disease in many cases suggest the importance in the treatment of allergic disease of therapeutic measures designed to restore the autonomic functional balance. The reactions of the adrenergic and cholinergic nerves to the various pharmacologic agents referred to above in the discussion of pharmacodynamic tests of autonomic function also suggest the rationality of the use of sympathetic stimulants and parasympathetic depressants.

The beneficial effect of sympathetic stimulation in the presence of cholinergic hyperactivity is illustrated by the relief obtained in cases of severe asthma by the administration of adrenin or ephedrin. Hyperirritability of the vagus reflex arcs in these cases is indicated by the spastic contractions of the bronchial musculature. The edema of the nasal and bronchial mucous membranes also indicates hyperstimulation of the cholinergic vasodilator nerves in these areas. The relief obtained by the administration of sympathomimetic agents can be explained most satisfactorily on the assumption that the existing cholinergic stimulation has been overcome by adrenergic stimulation of sufficient intensity. The advantage of repeated relaxation of the bronchial musculature by sympathetic stimulation in cases of intractable asthma, according to Barach<sup>2</sup>, may be explained on the assumption that a viscous cycle of bronchial spasm has been overcome by the repeated removal of the stimulation of the muscle receptors during the intervals of relaxation. The increased vascular tonus in the mucous membranes during these intervals also results in decreased capillary permeability, thus limiting the serous output of the glands.

Antibody-allergen reactions obviously are closely related to the specific

immune reactions. The nervous regulation of the latter is mediated mainly through the cholinergic nerves. Experimental data reported by various investigators, particularly Belak and his collaborators, indicate that the production of immune substances is influenced through both the adrenergic and the cholinergic autonomic nerves. In summarizing the results of investigations begun in 1925, carried out by his collaborators and himself, Belak<sup>4</sup> proposed classification of the immune substances, with respect to their relationships to the autonomic nerves, in two categories: sympathetic and parasympathetic. The first category includes the essential nonspecific antibodies, such as the alexins, opsonins, complement, etc., which are always present. Their production is augmented by sympathetic stimulation and inhibited by parasympathetic stimulation. The second category includes the essential specific antibodies, such as antitoxin, precipitin, agglutinin, lysine, etc. The production of these substances is augmented by parasympathetic stimulation and inhibited by sympathetic stimulation.

Other experimental and clinical data which support this point of view are not wanting. In experiments reported by Illenyi and Borzsak<sup>21</sup>, the hemolysin titer was increased by stimulation of the parasympathetic nerves, when the antigen was injected, and decreased by parasympathetic paralysis or stimulation of the sympathetic nerves. The inhibitory effect on hemolysin production of sympathetic stimulation was more marked than that of parasympathetic paralysis. The onset of infectious disease, as indicated by fever, increased metabolism, leukocytosis, etc., is accompanied by sympathetic hypertonus, whereas during the period of recovery, as indicated by the return to normal body temperature, decreased metabolism; disappearance of leukocytosis, increased alkali reserve, etc., parasympathetic tonus gains the ascendancy. At the beginning of an infectious process, therefore, resistance is decreased due to the increased sympathetic tonus which inhibits the production of the specific immune substances, whereas during the later phases resistance is increased due to increased parasympathetic tonus which augments the production of the specific immune substances.<sup>12,19</sup>

The nonspecific immune substances, according to Belak, are related to the emergency functions of the sympathetico-adrenal system which responds automatically and promptly to psychic stimulation, pain, muscular exercise, blood pressure, cold and various other changes in the internal and external environments. The relationship of the immediate reactions to infection, intoxication, et cetera, to the sympathetico-adrenal system, therefore, is biologically significant. The biological significance of the relationship of the production of specific immune substances to the parasympathetic system is less apparent.

The concept of the regulatory influence of the sympathetic nerves in the production of the nonspecific immune substances and that of the parasympathetic nerves in the production of the specific immune sub-

stances, as formulated by Belak, undoubtedly expresses a fundamental biologic relationship but cannot be regarded as strictly accurate in the light of our present knowledge of the anatomical distribution of the nerves of sympathetic and those of parasympathetic origin and the role of the neurohumoral mediators. Belak's conclusion that the nonspecific immune substances are related to the emergency functions of the sympathetico-adrenal system is well founded. The specific immune substances undoubtedly are related to cholinergic nerves both of sympathetic and of parasympathetic origin which respond to cholinergic (parasympathetic) stimuli according to a common mode.

Since the antibody involved in any antibody-allergen reaction must be regarded as specific, the nervous regulation of its production, according to Belak's theory, must be mediated through the parasympathetic or cholinergic nerves. Sensitization to a specific allergen undoubtedly involves increased cholinergic stimulation. This further emphasizes the importance of measures designed to restore the functional autonomic balance in the treatment of allergic disease.

The administration of sympathetic stimulants or parasympathetic depressants must be regarded as essentially palliative measures, since their effects usually are of short duration. Complete or permanent restoration of the autonomic balance probably cannot be achieved by these means.

It is significant to point out in this connection that parasympathetic or cholinergic hyperactivity is accompanied by a shift in the acid-base balance toward acidity and adrenergic hyperactivity by a shift in the acid-base balance toward alkalinity. Conversely, changes in the acid-base balance are accompanied by corresponding changes in the autonomic functional balance. The acid-base balance, consequently, plays a significant role in all diseases in which the autonomic nerves are directly involved.

The mechanisms of acid-base balance and water regulation represent the physical and chemical phenomena upon which depend the constancy of the liquid environment of the tissue cells which limits within a narrow range the variations in osmotic pressure, chemical reaction, fluid volume, ionic concentration, etc. The ions involved are mainly those of the electrolytes sodium, potassium and calcium. Potassium constitutes the intracellular base; sodium, the base of the extracellular fluids. Calcium is essentially acid. Sodium, potassium and calcium are neutralized or counterbalanced in their physiological ratios by the physical action of one ion upon another regardless of which salts of these electrolytes are present.

The body fluids normally are slightly alkaline. Actual acidity of these fluids, as is well known, is incompatible with life. Acidosis, as this term is commonly used, implies only decreased alkalinity. Since the total quantity of acid radicals derived from an ordinary diet greatly exceeds the intake of fixed base, conservation of base is highly important and depends largely on the functional state of the kidneys. Regulation of the water balance depends on the retention of electrolytes, particularly sodium, in appropriate

concentration. This is accomplished either by the conservation of base or by the excretion by the kidneys of excess base.

The results of clinical studies reported by Hollo and Weis<sup>20</sup> have demonstrated that calcium chloride administered intravenously in therapeutic doses reduces the bicarbonate content of the blood plasma but increases the H-ion concentration of the blood and the alveolar carbon dioxide tension in the lungs. The bicarbonate content of the blood plasma also is reduced by the administration of calcium chloride and calcium lactate by mouth. The results of animal experiments reported by Fürst<sup>13</sup> and others also show that the acid-base balance is shifted toward acidity by the administration of calcium and that an increase in the potassium-ion concentration results in a shift in the acid-base balance toward alkalinity. According to Reid<sup>29</sup> the acid-base balance in the blood plasma may be restored by the intravenous administration of sodium chloride regardless of whether the imbalance represents a shift toward alkalinity or toward acidity.

These data suggest the possibility of restoration of the acid-base balance in allergic patients by simpler measures, such as ordinary alkali therapy and appropriate diet, adapted to the requirements of every individual patient on the basis of a study of his or her physiological reactions. In cases with marked emotional factors appropriate psychotherapy is indicated, since the emotional states which tend to precipitate allergic reactions commonly are accompanied by a shift in the acid-base balance toward acidity. In peptic ulcer patients and many normal subjects, according to Mittelman and Wolff<sup>27</sup>, gastric acidity is increased during periods of experimentally induced anxiety, hostility and resentment, whereas pre-existing hyperacidity is decreased during periods of induced feelings of contentment and well-being.

Changes in the autonomic functional balance associated with induced changes in the acid-base balance have been amply demonstrated; consequently, restoration of the autonomic balance by appropriate therapeutic measures designed to restore the acid-base balance should not be regarded as beyond the range of possibility in many cases of allergic disease. Treatment directed toward the autonomic nerves primarily, if it results in restoration of the autonomic functional balance, will also affect the acid-base balance favorably. In cases with obvious emotional factors, appropriate psychotherapy, with or without reference to the acid-base balance, should be regarded as a useful adjunct to other therapeutic measures.

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## DERMATOLOGIC MANIFESTATIONS OF FAMILIAL NONREAGINIC ALLERGY

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IN previous communications on the general topic of familial nonreaginic allergy a few cases were described in which there were cutaneous lesions, which were found to be entirely controllable through mere avoidance of the allergens that caused specific tachycardia. My experiences have now included a sufficient number of such instances, perhaps, to warrant separate consideration of the group.

Today's presentation is not intended as finished proof of the importance of nonreaginic allergy as a cause of the several cutaneous manifestations that I shall mention. My selection of this topic was primarily a device or excuse for again directing your attention to the constant cardiac reaction which I have found to be so dependable a criterion of the nonreaginic allergic effect. I hoped also to arouse the interest of some of you in the possible applicability of that criterion to the specific diagnosis and relief of some cutaneous manifestations of allergy.

My experiences have impressed me with a fact that is already known to those dermatologists who are particularly interested in dermatologic allergy, namely, that the skin is *variously* affected by allergic disease. There are, indeed, some dermatologists who are convinced that the list of recognized cutaneous allergic manifestations will increase with further knowledge.

### CUTANEOUS CIRCULATION

A phenomenon of general significance that is sometimes apparent to the unaided eye is the favorable change in some patients in the arteriocapillary circulation after avoidance of all the pulse-accelerating allergens.

Previous to treatment the skin and nails may be pale and variously sallow, depending upon the pigmentation, and the nails may show a tendency to become wavy and cracked. The base of the nail may become loose, exposing the raw, bleeding surface of the nail-bed. The lips and the back of the hands may become chapped in winter and the thick skin of the fingertips at the sides of the nails may become cracked and bleeding.

That a deficient circulation is the chief cause of these latter lesions is evidenced by the fact that those of the hands can be in large part prevented or greatly improved if the patient merely keeps the hands quite warm at night by wearing soft and sufficiently thick cotton gloves in bed.

After successful treatment of the food-allergy the skin and nails become

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pink, the nails are no longer cracked, and the tendency of the skin to chap and to crack at the finger-tips disappears.

In one case (A.F.C.) the feet, previous to treatment, were constantly cold in winter and were slightly frost-bitten on one occasion. After treatment the feet have never been cold in winter, even when exposed to the lowest temperatures in the usual footwear (cotton socks).

#### SECRETORY ACTIVITY OF THE SEBACEOUS GLANDS

Some patients with familial nonreaginic allergy exhibit a constantly excessive secretory activity of the sebaceous glands, often associated with the development of comedones. In two patients this condition existed in a marked degree previous to treatment. Patient J. V., whose chief complaints were continual headaches, mild bronchial asthma and physical tiredness, characterized the condition of his nose with the expression "a grease-ball."

After successful dietary treatment the patient was relieved of all of his allergic symptoms, and the excessive activity of the sebaceous glands ceased.

In the second patient, also, the improvement in this respect was remarkable and permanent.

#### CHRONIC URTICARIA

It is common knowledge that chronic urticaria may be due to the eating of certain foods. Naturally, the culprit food has been easily identified only when it was the only excitant and if it was *not too frequently eaten*. Naturally, too, the foods that were so identified have been thought to possess some special urticariogenic property, and they are actually so listed by some writers, who advise avoidance of all of them by sufferers from chronic urticaria.

Study of the five cases, presently to be described, with the criterion of specific acceleration of the pulse has revealed the following tentative conclusions:

1. Chronic urticaria is at least frequently a symptom of familial non-reaginic allergy.

2. While it seems unlikely that any allergenic food will be found never to be urticariogenic, it seems to be a fact that among the list of an affected person's identified food allergens, some foods always or frequently cause urticaria, whereas others do so much less frequently, if at all.

3. Severe urticaria in some affected persons *seems* to be caused by inhaled allergen ("bed dust" in one of the cases described). However, this has not been proved.

*Case 1.*—January, 1940. J. G., male, aged thirty-six. Symptoms: incapacitating three-day headaches at one- to two-week intervals, frequent urticaria and angio-neurotic edema, and heartburn. All of these symptoms ceased completely and

# FAMILIAL NONREAGINIC ALLERGY—COCA

TABLE I. PULSE-DIET RECORD

Case 3.—C. G., aged fifteen

1944 Jan. 12	13	14	15	16	17	18
Pulse	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse
B.R.— 56	55	51	50	52	54	53
Br.— 67	72	78	60	60	62	64
30 m 79	84	76	58	63	63	66
60 m 77	88	72	58	62	63	65
90 m 78	88	72	57	63	63	68
Diet						
Shredded Wheat, sugar milk	toast milk	rice (boiled) salt	rice (boiled) salt	rice, butter egg, milk baked apple	rice, egg baked apple sugar milk	egg, rice baked apple sugar milk
Mid A.M.	88	65	59	65	62	
30 m 72	72	72	61	65	63	
60 m 64	64	70	60	64	64	
90 m 64	64	74	60	60	64	
Diet—	apple	apple	apple	carrot	carrot	
Lunch— 75	68	78	68	60	63	68
30 m 74	68	70	74	84	64	65
60 m 74	68	68	58	74	65	67
90 m 69	76	72	59	72	64	68
Diet—						
liverwurst milk, bread orange ginger-cookies	chicken, milk lettuce orange bread	2 eggs (boiled)	eggs (boiled)	veal rice milk baked apple	egg milk baked apple	egg milk baked apple
Mid P.M. 75	72	64	60	63		68
30 m 75	76	74	60	62		66
60 m 72	68	60	60	62		66
90 m 69	61	68	60	63		68
Diet—nothing	milk	milk	milk	baked apple milk		lettuce celery
Dinner— 74	74	64	60	63	65	68
30 m 69	85	61	62	64	65	70
60 m 65	78	63	63	64	64	69
90 m 66	—	62	62	62	67	72
Diet—chicken rice, milk cornstarch celery, carrot, lettuce	nothing	chicken	chicken, rice butter baked apple sugar, cream	chicken, rice butter baked apple milk, sugar	chicken potato milk baked apple	ham, potato carrot milk baked apple
Ret.— 65 hives today	hives 72	hives 58	hives less 60	no hives after lunch 63	no hives wt. 129 66	no hives wt. 128 64

permanently after wheat, cane sugar and coffee had been entirely eliminated from the diet.

Headache, accompanied with tachycardia up to 110 but *with no urticaria* nor heartburn, was induced by wheat eaten in quantity at the three meals of the test on one day. Heartburn without headache or urticaria and with a moderate tachycardia (90) followed a single ingestion of cane sugar (two tests).

Urticaria and angioneurotic edema with delayed headache and no heartburn followed the ingestion of coffee. There was only slight tachycardia (80); normal maximum 74.

Other cereals (rice and rye) caused no symptoms and only a slight tachycardia (80).

*Case 2.*—May, 1940. Mrs. A. P., aged seventy. Symptoms: marked chronic generalized *urticaria* ("dollar-size"), chronic cough, constipation, "heart attacks," fainting, weakness, tiredness, and occasional headaches. All of these symptoms ceased completely and permanently after the following foods had been entirely eliminated from the diet: beef, cow's milk, egg, corn, orange, olive, banana, yeast, proprietary laxative. The normal pulse range was found to be 70 to 74.

Urticarial attacks, accompanied with tachycardia up to 100, were induced sep-

# FAMILIAL NONREAGINIC ALLERGY—COCA

## TABLE I. PULSE-DIET RECORD (Cont'd)

Jan. 19	20	21	22	23	24	25
	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse
B.R.— 53	52	53	52	52	52	52
Br.— 65	63	62	—	59	59	59
30 m 67	64	64	—	60	60	60
60 m 66	63	63	—	59	58	60
90 m 67	65	65	—	—	59	59
Diet—banana egg, rice milk sugar	orange egg rice milk	grapefruit egg rice milk	no breakfast	Ry-Krisp banana milk	pineapple Ry-Krisp milk	pineapple Ry-Krisp milk
Mid. A.M.— 68	64	63	60	58	60	59
30 m 63	62	65	58	59	58	58
60 m 60	64	64	59	60	59	57
90 m 63	63	62	58	59	61	58
Diet—dates	dates	dates	tomato	chocolate bar	banana	raisins
Lunch— 62	64	61	60	59	60	59
30 m 63	65	60	61	60	58	60
60 m 64	63	62	59	61	59	59
90 m 65	64	61	60	60	58	58
Diet—egg milk baked apple sugar	egg milk lettuce baked apple	egg milk baked apple	ham broccoli baked apple milk	lamb chop potato, carrot broccoli, let- tuce, celery orange, apple milk	egg pineapple lettuce milk	lamb chop lettuce milk orange
Mid P.M.— 64	64	60	59	60	58	57
30 m 66	66	63	62	57	59	58
60 m 64	63	60	61	56	60	57
90 m 60	65	62	59	58	58	58
Diet—orange	prunes	prunes peanut-butter	prunes peanut-butter	tomato juice sugar	chocolate bar	raisins
Dinner— 62	64	61	59	58	58	59
30 m 67	61	62	58	59	60	61
60 m 65	60	60	59	57	59	66
90 m 62	62	62	60	58	60	60
Diet— ham, potato carrot, milk baked apple	ham, potato carrot str. bean baked apple	fish potato, car- rot, peas bsked apple	lamb chop potato, fleets orange, banana celery, milk	Ry-Krisp peanut-butter milk	lamb, potato onion, carrot lettuce, pars- ley, celery pineapple, date orange, Ry- Krisp	fish, potato onion, tomato broccoli, celery Strawberry milk
Ret.— 61	—	—	—	—	—	—
wt. 128	sore throat wt. 127	sore throat wt. 128	sore throat Tt. 127	sore throat "feeling sickk all day"	throat healed "feels well" wt. 127	wt. 126

arately by the following foods: beef, orange, banana, olive, egg, laxative, yeast, corn. All other cereals and cane sugar were tolerated without causing any tachycardia or other symptoms.

It is noteworthy that on the first day of the trial diet, exhibiting "large hives and a bad cough" on rising, the patient suffered no further urticaria, although she ate nothing on that day but beef, which caused an almost constant tachycardia reaching a maximum of 100, and which, some weeks later, at a single test, caused a severe urticarial attack. This again illustrates the depressing effect of continued allergic insults upon the reactive mechanism of a shock tissue. Not all the shock tissues are necessarily depressed at one time; this is seen in the fact that on that day there were, beside the tachycardia, "some coughing and dull headache."

*Case 3.*—January, 1944. C. G., female, aged fifteen. Symptoms: chronic urticaria, recurrent headaches, physical tiredness, occasional dizziness, and canker sores. The patient became symptom-free after the range of her pulse had been brought to her normal limits (52 to 61) through avoidance of her three food allergens—

## FAMILIAL NONREAGINIC ALLERGY—COCA

TABLE I. PULSE-DIET RECORD (Cont'd)

Jan. 26	27	28	29	30	31	Feb. 1
Pulse	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse
B.R.— 52	52	52	52	54	53	52
Br.— 58	57	59	59	65	60	60
30 m 60	58	58	90	63	58	58
60 m 67	59	57	86	62	60	59
90 m 61	57	58	86	62	59	60
Diet— strawberries Ry-Krisp milk	peaches cranberry rice milk	cranberry rice milk sugar	toast (wheat) peanut-butter apple milk	rice milk orange	Ry-Krisp applesauce milk	grapefruit oatmeal milk sugar
Mid A.M.—				61		
30 m				58		
60 m				58		
90 m				59		
Diet—				orange		
Lunch— 61	58	58	88	59	60	60
30 m 60	60	60	86	61	59	61
60 m 59	59	59	87	60	61	59
90 m 58	57	59	84	61	60	59
Diet— egg, lettuce celery, milk butterscotch	chicken corrot lettuce, milk orange	egg celery lettuce milk	lamb chop carrot, lettuce milk	pork potato str. bean celery, milk applesauce	chicken carrot, let- tuce, celery orange, milk	ham carrot milk orange
			"covered with hives; face swollen."			
Mid P.M. 57	57				60	60
30 m 58	58				59	59
60 m 58	57				58	58
90 m 57	58				59	60
Diet—orange	orange				raisins	apple
Dinner— 58	59	59	78	60	59	60
30 m 59	60	60	76	59	60	74
60 m 58	61	58	76	61	59	69
90 m 58	60	58	74	59	59	65
Diet—chicken peas rice milk	squash, potato lamb, lettuce Ry-Krisp peanut-butter	fish, squash tomato, onion celery, milk butterscotch	chicken, egg rice, potato celery, lemon milk	Ry-Krisp milk, peanut- butter applesauce rice-pudding	ham asparagus turnip, rice milk	corn, spinach pork, potato oatmeal, egg sugar, lemon juice
Ret.— 57	58	59	68	59	—	—
wt. 126	wt. 126	wt. 126	wt. 126	wt. 126 hives	few hives	no hives (head cold)

wheat, beef and strawberry. Other cereals and raspberry cause no tachycardia and no other symptoms.

Table I shows the daily pulse-diet record of C. G. for the first three weeks.

The slowing of the pulse after the evening meal on January 12 suggested that no allergenic food had been eaten at that meal. Hence, the marked tachycardia occurring after breakfast the following day was not attributed to milk but to the wheat (toast), which had not been eaten on the previous evening but which had been eaten on the previous morning, when also there was a subsequent moderate tachycardia.

Wheat was last eaten at noon on the 13th when the cardiac shock-tissue was in depression from the morning reaction. However, there was a marked, delayed effect in the evening (85), which continued in lessening degree through the next three days until it was overpowered by a fresh reaction caused by the eating of veal.

The urticaria which was present at the beginning of the dietary examination persisted into the third day.

The tachycardial reaction to veal continued into the sixth day (62 on January 22), yet there was no urticaria at any time in that period, nor any other symptom.

## FAMILIAL NONREAGINIC ALLERGY—COCA

In the following two days and in the third day until the evening meal (strawberry), the pulse-rate did not exceed the normal maximum (61).

Strawberry in two tests caused only a very slight tachycardia and no urticaria nor other symptom.

After another two days (January 27, 28) in which the pulse-range remained normal, a final test of wheat was made, resulting in a marked tachycardia, which lasted only twenty-four hours. The accompanying urticaria and angioneurotic edema continued for another day.

The tachycardia occurring after dinner on February 1 was believed to be an effect of the brief attack of common cold. The patient is not sensitive to corn.

There was a loss of four pounds in weight in less than four weeks—probably fluid.

The etiological study of chronic urticaria is complicated by the occasional instances of spontaneous recovery, or of a lessening of the severity of the condition. This occurrence prevented a definite conclusion as to the cause of the urticaria in the fourth case.

*Case 4.*—A. McC., female, aged thirty-two. First consultation, May, 1943. The patient exhibited nine of the most common symptoms of food allergy but complained chiefly of chronic urticaria, which was severe only in the night, regularly preventing sleep after midnight. The pulse was erratic, ranging from 60 to 83, but the rates above the estimated normal maximum of 74 could not be ascribed to any item of diet. This fact and the constant recurrence of the nocturnal attacks suggested an environmental allergen, possibly bed dust or feathers.

Dust-proof covers were applied to bed mattress and pillows in June, 1943, and the nocturnal attacks immediately ceased. Thereafter, only occasional wheals appeared in the daytime and dermatographism persisted.

In March, 1944, the dust-proof covers were removed, but thereafter there has been no recurrence of the nocturnal attacks, although one or two wheals still appear in the evening as before. The pulse is still erratic.

### *Additional Note*

Still not being satisfied with the improvement noted in the foregoing, the patient decided to undergo the conservative sympathectomy performed by Dr. Max Danzias and described in an earlier report.<sup>1</sup> The operation was done on June 27, 1944, and healing of the wound was rapid and uneventful. There was some pain in the thigh (inner aspect) on the side of the operation, which gradually disappeared.

There were a few hives on the day of the operation but none whatever at any time since.

The pulse, which before the operation had ranged erratically between 65 and 84, now shows a normal range of 65 to 76 on a large dietary list. After an evening meal containing onion and parsley (offender not yet further identified), the pulse-rate reached 80 with carry-over effect to the same point on the next morning.

*Case 5.*—Mrs. S. W. C., 1942, aged forty-seven. Symptoms: chronic urticaria (for one year), migraine, constipation. B. P. 128/76. Pulse range before treatment 66 to 100. Normal range, 56 to 66. Pulse-accelerating allergens: egg, citrus fruit, cereals, cane sugar, banana, plum family, fish, beef, lamb.

After avoidance of these foods the severity of the urticarial attacks was decidedly lessened but they did not cease, and the pulse record shows the effect of some extradietary allergen, probably environmental. The patient was so much better that she would not take the trouble to try to identify this allergen. She reports recently that she no longer restricts her diet and her urticaria is relatively negligible.

# FAMILIAL NONREAGINIC ALLERGY—COCA

## TABLE II. PULSE-DIET RECORD

Case 5. Mrs. S. W. C., aged forty-seven

1942 Feb. 2	3	21	28	Mar. 1	3	9
Pulse	Pulse (hives)	Pulse (few hives)	Pulse	Pulse	Pulse	Pulse (hives)
B.R.— 67	78	62	58	56	60	58
Br.— 70	80	68	66	72	74	64
30 m 78	98	68	68	74	72	64
60 m 82	86	66	66	74	80	64
90 m 84	87	60	66	84	72	64
Diet— corn flakes sugar	2 eggs (more hives)	bacon milk coffee	bacon milk coffee	bacon milk	bacon milk (hives)	milk
Mid A.M.— 82	78					
30 m 72	90					
60 m 76	96					
90 m 82	82					
Diet—milk (headache)	grapefruit (recurrence of hives)					
Lunch—	84	60	66	60	66	64
30 m 74	74	60	66	60	74	64
60 m 88	74	68	66	64	74	64
vomited —						
90 m 66	—	62	66	64	70	64
Diet—lamb peas	pork carrot	peas carrot Lima beans	beets celery cheese tea	ham, tomato str. beans celery grapes coffee (hives)	chicken peas spinach	chicken str. beans carrot
Mid. P.M.	84		62			
30 m 90	90		68			
60 m 88	88		66			
90 m 80	80		—			
Diet—	banana (hives)		chocolate peppermint (hives)			"hives today"
Dinner—	80	64	64	58	68	64
30 m —	84	64	64	60	68	64
60 m —	80	66	64	62	66	64
90 m —	78	66	64	62	66	64
Diet—(aspirin)	chicken str. bean	chicken potato str. bean Vi. B. Com- plex (few hives)	chicken, tomato, carrot grapes Vi. B. (few hives)	chicken ham milk	ham carrot potato celery (hives in night)	chicken potato peas coffee
Ret.— 8½ 1st day, test	78	—	—	—	—	—

## ATOPIC DERMATITIS

The pulse-controlled dietary method has been applied in a few cases of atopic dermatitis with inconclusive but, on the whole, encouraging results.

## SUMMARY

Observations are reported indicating that familial nonreaginic food allergy may cause:

(1) Significant disturbance of the general peripheral circulation (pallor, "chapped" skin, tendency to chilblain or frostbite); (2) abnormalities of the nail; (3) excessive secretion of the sebaceous glands of the skin; and is a frequent cause of (4) chronic urticaria.

## REFERENCE

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## DISCUSSION

DR. LESTER REDDIN (Pearl River, N. Y.): Although the symptoms that I have exhibited, that is, at least prior to September, 1940, are not dermatologic, merely as a matter of interest, Doctor Coca thought it might be well to mention the non-dermatologic symptoms which I have experienced.

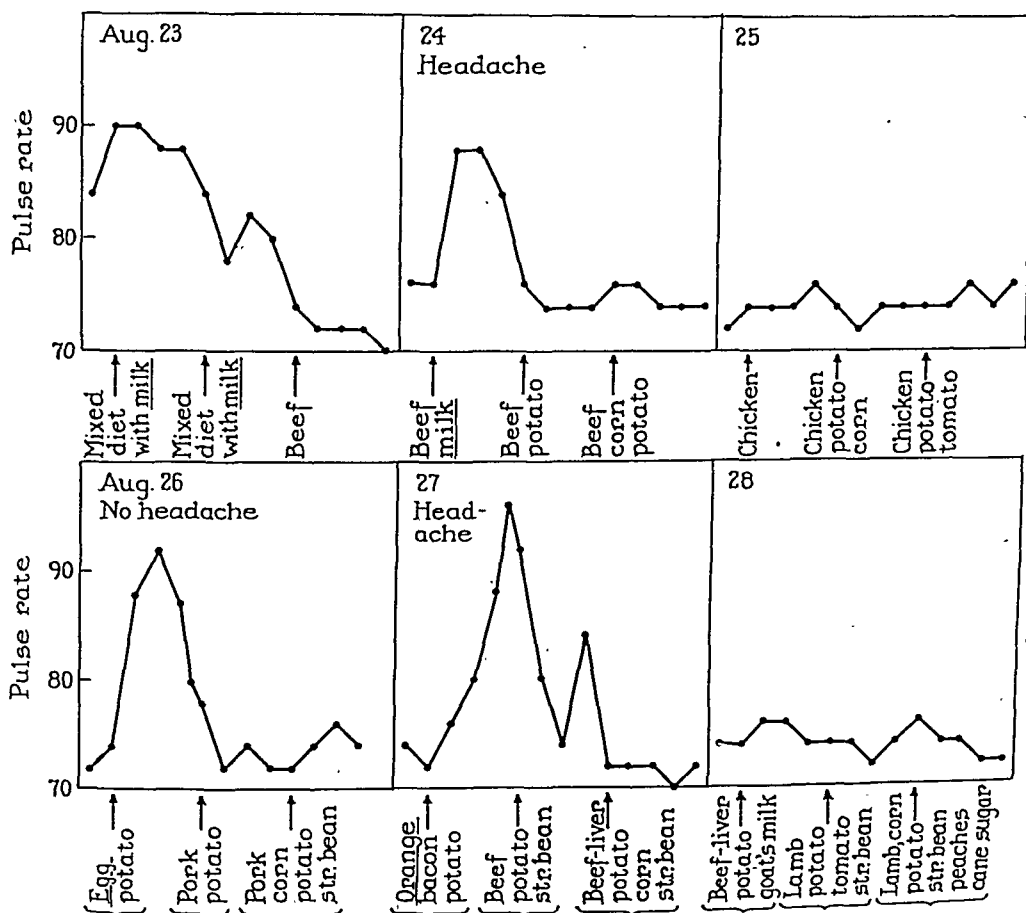


Fig. 1.

Prior to 1940, that is, September 1940, I had been suffering for some years with chronic sinusitis, dizziness on occasions, migraine and tachycardia, which, while I was in college, prompted the cardiologist there at the health service of the university to keep me under observation for several months. In the summer of 1940 I was experiencing quite a bit of difficulty with rhinitis in the evenings especially, and inasmuch as I worked with animals, my family physician suggested that I see Doctor Coca and have certain skin tests done for danders.

All of the skin tests for danders as well as for foods were negative. There was no local reaction to any of them. We then followed out the trial diet, taking the pulse record for two days with the general diet which I had been following, getting the range of pulse which I had experienced with that general diet. Then we limited the diet to beef and established the normal pulse rate. From then on, every day after

the pulse again returned to normal following an attack from an excitant, a new food was added.

On the first day when the mixed diet was fed, including cow's milk, the pulse range was up to 90 (Fig. 1). That evening the diet was limited entirely to beef, and a normal pulse rate was established. The second morning beef and milk were again eaten, and the pulse ran up close to 90. After it returned to normal, potatoes were added, with no apparent increase in the pulse rate, and that evening another food was added—corn. On the day of the 25th the pulse remained within what has now been established as the normal limit for myself, the variations being anywhere from 70 to 76. Regardless of the time of day or the digestive activity, that pulse remains very constantly in those limits.

You can also see that following the milk, there was very severe migraine. For breakfast the morning of the 26th eggs were added and again a tachycardia persisted, although no headache or any other symptoms were shown. Throughout this entire time the rhinitis, or rather the chronic sinusitis had been continuing. There was no improvement of that during the test. The next food to be added which caused a very prompt rise in the pulse rate was orange, which also caused a mild migraine. Various other foods were added from time to time throughout the few days that I was under examination, with no effect whatsoever. So that in the whole course of the examination, which was around four days, a very short case, I had eliminated all of the foods from the diet which were allergenic.

The sinusitis prior to the trial diet had been treated by the various methods without surgery as well as culturing and staphylococcic therapy. None of the means of therapy gave me lasting results. Following the trial diet there was not very much improvement by avoiding the allergic foods, but toxoid therapy was again resumed, and this in conjunction with avoidance of the allergic foods gave complete recovery within about two months, so that sinus plates taken in January showed absolutely no signs of any inflammation of the sinuses. The plates were taken at our local hospital.

Although I am not as good as some of Doctor Coca's other patients, I avoid the allergenic foods pretty well. There are occasions when I dissipate and suffer somewhat from that dissipation. There were no skin lesions at all throughout the whole study, so, unfortunately, I am not talking on this subject today, but that is the picture as I have seen it and as Doctor Coca has interpreted it from my pulse rate.

*Frequency of Allergy in Orthodontic Patients.* Straub, W. J.: Eye, Ear, Nose & Throat Monthly, No. 31, 1944.

The author reviews the literature as it is applied to the production of abnormal facies, growth and development in allergic children. In the present study, 104 patients of the orthodontic division (fifty-eight female and forty-six male) were completely investigated from the allergic standpoint. Forty-one (39.4 per cent) were definitely allergic, thirteen (12.5 per cent) were borderline and fifty (48.1 per cent) were negative upon the basis of history and skin tests. Various other medical conditions (allergic and nonallergic) were distributed among these patients. Blood studies showed eosinophilia in seventy-four patients. Of the forty-one patients with chronic nasal allergy, twenty-four (61.5 per cent) had contracted maxillary arches with accompanying protraction of the anterior teeth and retraction of the mandible or mandibular teeth. This high percentage suggests that in most cases of nasal blockage, associated with facial deformities, allergy must be suspected and considered definitely related to the development of dento-facial anomalies. Bibliography. L. J. H.



# AGGLUTINATION OF POLLEN-ANTIGEN-COATED BACTERIA BY SERA OF RAGWEED-SENSITIVE PATIENTS

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AN unusual method was used to study agglutinins in the sera of known ragweed-sensitive patients. It was demonstrated by Jones<sup>1</sup> that antigenic properties can be transferred. Thus, bacteria, after being coated by a test antigen, were agglutinated by an immune serum corresponding to that antigen. For example, Roberts and Jones<sup>2</sup> adsorbed a specific antigen, horse serum, upon bacteria which were subsequently agglutinated in the presence of a specific antibody, anti-horse serum, even in high dilutions. An attempt was therefore made to transfer the antigenic properties of ragweed pollen, or its extract, upon *Serratia marcescens* (*Bacterium prodigiosum*) and to test against the treated bacteria the sera from ragweed-sensitive patients.

*Serratia marcescens* was chosen as a recipient of the antigenic properties of ragweed pollen because (1) it is non-pathogenic; (2) its presence in suspension is easily demonstrable; (3) its agglutination may be easily visible macroscopically; (4) a specific antibody for it, as a rule, has not been found in human sera. Twenty-four-hour-old cultures (grown at room temperature to obtain red colonies) were used throughout the experiment. The antigens used were giant and dwarf ragweed pollens.

The sera for controls were obtained from volunteers known to be non-allergic and on whom intracutaneous tests to ragweed pollen extract were negative.

In order to determine the optimum conditions for transference of antigenic properties upon the bacteria, the following bacterial preparations were made:

1. One gram of ragweed pollen was added to 10 c.c. of a suspension of *Bacterium prodigiosum* in sterile distilled water.
2. One gram of ragweed pollen was added to 10 c.c. of a suspension of *Bacterium prodigiosum* in sterile distilled water heated to 60° C. for five minutes.
3. One gram of ragweed pollen was added to 10 c.c. of a suspension of *Bacterium prodigiosum* in sterile distilled water phenolized to 0.4 per cent.
4. One gram of etherized ragweed pollen was added to 10 c.c. of a suspension of *Bacterium prodigiosum* in sterile distilled water.
5. One gram of etherized ragweed pollen was added to 10 c.c. of a suspension of *Bacterium prodigiosum* in sterile distilled water heated to 60° C. for five minutes.

<sup>1</sup>From the Department of Laboratories and the Department of Allergy, Israel Zion Hospital, Brooklyn, N. Y.

6. One gram of ragweed pollen washed in 10 per cent formalin was added to a 10 c.c. suspension of *Bacterium prodigiosum* in sterile distilled water.

7. One gram of ragweed pollen washed in 10 per cent formalin was added to 10 c.c. of a suspension of *Bacterium prodigiosum* in sterile distilled water heated to 60° C for five minutes.

8. *Bacterium prodigiosum* was suspended in 10 c.c. of a 1:100 dilution of ragweed extract (a 50 per cent glycerinated Coca's solution with 0.4 per cent phenol).

9. *Bacterium prodigiosum* was suspended in 10 c.c. of a 1:100 dilution of ragweed extract in Coca's solution.

10. *Bacterium prodigiosum* was suspended in 10 c.c. of a 1:100 dilution of a saline extract of ragweed pollen.

All suspensions of bacteria and ragweed antigen were allowed contact for twenty-four hours in an incubator at 37° C. and were subsequently placed in a refrigerator until ready for use. All bacterial suspensions with pollen antigen were then centrifuged to separate the pollen from the bacteria. The bacteria were washed with sterile normal saline solution, and then resuspended in sterile normal saline solution just before tests were made. The opacity of approximately one billion organisms per cubic centimeter was used as a standard. Microscopic examination of each bacterial suspension was made to rule out the presence of pollen granules or clumping of bacteria.

The tests were performed as follows:

1. Test tubes with 1 c.c. of serum from ragweed-sensitive patients were arranged in serial dilutions in racks (in sterile normal saline solution) of 1:10, 1:20, 1:40, 1:80, 1:160, 1:320.

2. Test tubes with 1 c.c. of serum from non-allergic patients were similarly arranged in serial dilutions.

3. One c.c. of a pollen-antigen-coated bacterial suspension was added to each test tube of the series of dilutions as made above.

4. Thorough mixing was obtained by shaking the racks for a few minutes.

5. All racks with the test tubes were placed in an incubator at 37°C for two hours and a preliminary reading was made.

6. All racks were then placed in the refrigerator over night. The next morning, they were removed and allowed to stand at room temperature for one hour before final readings were made.

7. Readings were done macroscopically as well as microscopically. Agglutination of *Bacterium prodigiosum* is easily read macroscopically.

The results were:

1. No agglutination of any of the pollen-antigen-coated bacterial suspensions was observed with any of the ten control sera (from the non-allergic patients).

2. With the sera of known ragweed-sensitive patients agglutination was observed in the following pollen-antigen-coated bacterial suspensions listed above as:

- No. 1— 2 sera in dilutions up to 1:20  
24 sera in dilutions up to 1:40  
3 sera in dilutions up to 1:80
- No. 2— 2 sera in dilutions up to 1:20  
24 sera in dilutions up to 1:40  
3 sera in dilutions up to 1:80
- No. 4— 1 serum in dilution up to 1:20  
24 sera in dilutions up to 1:40  
4 sera in dilutions up to 1:80
- No. 5— 1 serum in dilutions up to 1:20  
24 sera in dilutions up to 1:40  
4 sera in dilutions up to 1:80
- No. 6—11 sera in dilutions up to 1:20  
16 sera in dilutions up to 1:40  
2 sera in dilutions up to 1:80
- No. 7—11 sera in dilutions up to 1:20  
16 sera in dilutions up to 1:40  
2 sera in dilutions up to 1:80
- No. 9— 3 sera in dilutions up to 1:20  
23 sera in dilutions up to 1:40  
3 sera in dilutions up to 1:80

3. No agglutination was observed in pollen-antigen-coated bacterial suspensions listed as No. 3, No. 8, and No. 10 with any of the sera of the known ragweed-sensitive patients.

It may be inferred from this experiment that (1) the presence of agglutinins was demonstrated in sera of known ragweed-sensitive patients; (2) the antigenic property of ragweed pollen was transferred to bacteria. However, the low titer of agglutination is not very conclusive.

It remains for further investigation to determine (1) if there are any other factors which may influence a fluctuation of the titer of agglutination of pollen-antigen-coated bacteria by sera of ragweed-sensitive patients; and, (2) if, after specific therapy in ragweed-sensitive patients, changes in the titer of agglutination occur.

If the above method can be improved for the detection of agglutinins in sera of known ragweed-sensitive patients against pollen-antigen-coated bacteria, then, perhaps, other agglutinins in other allergies may be demonstrated.

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## MILITARY ASPECTS OF ALLERGIC RHINITIS

MAJOR PHILIP BLANK, MC  
and  
CAPTAIN HARRY LEVITT, MC

AN increasing interest in the problems of allergy by the armed forces<sup>3,5,8,16</sup> has been evidenced by the large number of allergy sections and clinics established in various Army hospitals and by the recognition of allergy as a medical specialty by the Navy. With this increased interest comes a need for more specific and detailed knowledge of the many difficulties that beset this new field of Military Allergy. It is the purpose of this paper to discuss the military problems involved in the study of allergic rhinitis.

Allergic rhinitis is a "harassing" disease. It causes tremendous loss of efficiency and may cause much loss of time. Soldiers suffering this affliction haunt the eye, ear, nose and throat clinics without much relief from their symptoms unless an allergic regime is instituted. This disease is often misunderstood in the various military organizations and gives the soldier not only a physical handicap but also a great mental hurdle to overcome. He is often branded a "goldbrick."

The term allergic rhinitis refers to a syndrome of sneezing, rhinorrhea, and nasal obstruction due to hypersensitivity to various antigens. It may be perennial or seasonal in nature. Many and various terms have been applied to this syndrome, some pertaining only to the perennial type of allergic rhinitis and others only to the seasonal type. Among these terms are found vasomotor rhinitis, perennial rhinitis, paroxysmal rhinitis, allergic coryza, allergic rhinopathy, hay fever, rose fever, summer catarrh, pollenosis and many others. No term suggested to date has been completely satisfactory to all, therefore, the terms used in this discussion are defined. The term allergic rhinitis will refer to all cases of rhinitis having an allergic etiology; perennial rhinitis will refer to those cases that are perennial in nature without undue seasonal variation and not due to pollen and the term hay fever will refer to seasonal allergic rhinitis due to pollen. The term hay fever may be qualified by adding the name of the season in which it occurs or by the name of the plant which produces the pollen. This choice of terms is only because of popular usage and simplicity.

The military problem of allergic rhinitis involves not only the diagnosis and treatment of these cases, but also the applicability of treatment and the disposition of these patients. In other words, what should be done with a soldier suffering from allergic rhinitis and what prognostication can be made concerning his reaction in various places under various conditions.

The incidence of allergic rhinitis among military personnel is noted

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# ALLERGIC RHINITIS—BLANK AND LEVITT

TABLE I. CASES OF ALLERGIC RHINITIS SEEN AT FORT EUSTIS, VIRGINIA  
(June 1, 1941 to December 31, 1943)

	Number of Treated Cases	% of Total Cases	Incidence per 1000 Men
Fall hay fever	303	41.0%	2.58
Fall hay fever and perennial rhinitis	22	3.0%	0.19
Fall hay fever and asthma	39	5.4%	0.33
Fall hay fever, asthma and perennial rhinitis	1	0.1%	0.01
Summer hay fever	75	10.2%	0.64
Summer and fall hay fever	60	8.1%	0.51
Summer hay fever and perennial rhinitis	13	1.7%	0.11
Summer hay fever and asthma	14	1.8%	0.13
Summer and fall hay fever and perennial rhinitis	9	1.2%	0.08
Summer and fall hay fever and asthma	13	1.7%	0.11
Perennial rhinitis	155	21.0%	1.32
Perennial rhinitis and asthma	37	4.8%	0.31
Total	741	100.0%	6.32

in Table I. In this table the various syndromes and combinations of syndromes are tabulated. They represent only the group of cases seen at the Allergy Clinic at Fort Eustis, Virginia, from June 1, 1941, to December 31, 1943.

A total of 741 cases of allergic rhinitis was seen at this clinic and represents an incidence of 6.3 per 1,000 men. Although this figure is lower than is usually quoted as the incidence of allergic rhinitis, it must be remembered that many of the more severe cases are rejected for military service by the induction boards and many of the milder cases do not report for treatment or are not recognized as allergic sufferers. Therefore the figure 6.3 per thousand does not accurately represent the incidence, but rather represents the number of men who received allergic care because of allergic rhinitis at Fort Eustis, Virginia.

Clinically uncomplicated fall hay fever due to ragweed pollen represents 41 per cent of the allergic rhinitis cases. These cases had no clinical manifestation of sneezing, nasal congestion or rhinorrhea at any time except during fall hay fever season. Of these 303 cases, 100 cases showed marked or moderate skin sensitivity to ragweed pollen alone, while 193 cases showed moderated or marked skin sensitivity to other inhalants. Forty-six cases showed a greater skin sensitivity to other inhalants than to ragweed pollen, while ten cases showed no skin sensitivity at all. However, these latter cases showing no skin sensitivity showed sensitivity of the nasal mucosa or conjunctiva or both to ragweed pollen on contact.

Twenty-two cases of fall hay fever were complicated by evidence of perennial rhinitis. These cases were all clinically fall hay fever but on close questioning gave a history of attacks of allergic rhinitis at times other than the hay fever season.

Thirty-nine cases of fall hay fever were complicated by asthma, seventeen of these cases had seasonal asthma coming on towards the end of the season while twenty-two cases had occasional mild perennial asthma. The latter cases were not classified primarily as asthma because of the

mildness and the infrequency of their asthmatic symptoms. These patients gave a history of wheezing only on close questioning and the majority of them did not realize they had asthma. Ordinarily this type of rhinitis would pass as simple hay fever. It is important from a military standpoint to distinguish complicated from uncomplicated cases because of the effect of nonspecific factors in the future behavior of these men.

Sixty cases gave clear-cut histories and findings of both grass and ragweed hay fever with a period of relief between two attacks.

Summer hay fever due to grasses was found in seventy-five cases. These patients had no symptoms except during the season of grass pollination but again many multiple skin sensitivities were found. The incidence of multiple skin sensitivities was greater in this group than in the ragweed group. Although the summer hay fever cases were on the whole clinically milder than the ragweed cases, more complications such as perennial rhinitis and asthma were found. There were more clinically complicated cases of summer hay fever (109 cases) in relation to clinically uncomplicated cases (75 cases) than there were clinically complicated cases of fall hay fever (122 cases) in relation to uncomplicated cases of fall hay fever (303 cases). The grass hay fever cases represent a more difficult problem to our overseas forces than do the ragweed hay fever cases because of the more universal distribution of grasses and the higher incidence of complications in this group.

In this clinic spring hay fever due to trees was not seen except for one case of oak sensitivity combined with grass sensitivity. We feel that this is purely coincidental and a result of the short duration of the tree season. A few cases due to molds were seen but the clinic was inadequately prepared for intensive mold studies and therefore this group of cases is not reported in this paper.

One hundred fifty-five cases of perennial rhinitis were seen in this clinic. The majority of these cases were due to inhalants only, there being only twelve cases which were definitely proven to be due solely to foods. Studies for bacterial antigens were unsatisfactory because of the lack of bacterial antigens on hand. Most cases were sensitive to dust but clinical sensitivities to pyrethrum, feathers, orris root, pine sawdust, tobacco, and animal danders were rather frequent.

All cases of perennial rhinitis received an x-ray study of their sinuses. In all but twenty cases evidence of pathology in the sinuses was found on x-ray examination, and was mainly evidenced by a thickening of the mucous membranes; hypertrophic sinusitis. Some degree of polyposis was found in thirty-two cases. Two cases of perennial rhinitis were associated with a generalized pruritis which disappeared during treatment of the rhinitis without local or any other general treatment. One case of perennial rhinitis was associated with a marked seborrhea; both conditions were controlled by the elimination of cottonseed oil, corn and grapefruit from his diet.

The cases of perennial rhinitis with asthma represent those cases having had only very slight wheezing attacks, this symptom being elicited only on detailed history. This group probably should be listed as extremely mild asthmatics but because their symptoms were practically entirely upper respiratory they are listed as rhinitis cases rather than asthmatic cases.

In military allergy, as well as in civilian practice, the precise etiologic diagnosis of hay fever requires a knowledge of the pollens to which the patient is exposed. This requires a knowledge of the identity of those plants in the patient's vicinity which are capable of producing symptoms. It is not only necessary to know the identity of plants but also their relative prevalence and the average onset and termination of their pollinating seasons. The military surgeon dealing with allergic diseases must have some knowledge of the plant flora in any locale that the Army finds itself. Thus, in this day of universal warfare, a knowledge of the plant flora throughout the world is necessary. An attempt has been made in a general way to tabulate the more important causes of hay fever in various parts of the world with the realization that such a tabulation must be extremely general because of the lack of material from many parts of the world and the lack of space in a paper such as this. Nevertheless, for clinical and practical purposes, single cities or areas are taken as typical for large districts to contain a certain type of flora with pollination seasons which with some variation are by and large uniform for that area.

Pollen data for the United States<sup>7,10</sup> are abundant and easily obtained. The main facts concern ragweed and grasses, but it must be remembered that many other plants, trees, and molds can be important factors in the etiology of hay fever.

Ragweed is found in a belt bounded roughly by the Great Lakes and the forested area north of them, the Appalachian Mountains, the Gulf of Mexico and the hundredth meridian, with the heaviest recorded production in Indiana. Most of the ragweed pollen is produced by short ragweed and giant ragweed. The other ragweeds are mainly of local or sectional importance. While western and false ragweed may begin pollination in the southwest as early as May 15 the real ragweed season begins abruptly during the second week of August in the whole area east of the Rocky Mountains and north of Arkansas and Tennessee. In the southern states the onset of the season is from one to four weeks later than in the north. The pollen storm reaches its height earliest in the high dry region of the upper Missouri Valley about August 25, which is about a week earlier than in the north half of the Mississippi Valley and the Great Lakes region. By the first of September the center of the storm has begun to move southward reaching south Texas about October 1. The early approach of cool weather in the Dakotas, Montana and Wyoming limits heavy ragweed pollen production to about thirty

days. The average length of the season in the central and southern states is from forty-five to fifty days, with an extreme range of possible exposure of very sensitive hay fever sufferers in Brownsville, Texas; southern Arizona and northeastern Mexico of six months, May 15 to November 15.

Grasses are almost universal in their distribution. There are many species of grasses, the more important being Timothy, Bermuda, June, Orchard, Johnson, Red Top and Sweet Vernal grass. It is usual to find Timothy grass predominating in colder or temperate climates and Bermuda grass predominating in the warmer areas. The period of pollination depends on the climate; for example, certain grasses may be perennial pollinators in southern California while others have a definite period from May through June in some of the more northern states. The reader is referred to the many excellent papers concerning plant pollination in the United States for more detailed data.

Outside of the United States the main offender producing hay fever is grass pollen. Ragweed<sup>1</sup> is seldom, if ever, found in Alaska, British Isles, Scandinavia, Belgium, Holland, Germany, Portugal, Spain, Italy, India, Burma, the Malay Peninsula, Indo-China, China proper, the Philippines, Egypt, South America or Africa. In general, the colder countries have a high proportion of Timothy grass and the warm countries have a preponderance of Bermuda grass. Trees and local vegetation are factors usually of minor importance except in definite localities. The main offenders are here noted in a rather general summary.

In the British Isles<sup>17</sup> the pollen season extends from February to the end of October and falls into three main phases dominated by trees, grasses and herbaceous dicotyledons, respectively. Of the trees the most important are Birch, Yew, Oak, Elm, Hazel and Alder. The tree season extends to about the end of April. The grass season starts early in June, reaches a peak late in June and extends to about the end of July. The grass season is by far the main hay fever season. The herbaceous dicotyledons are of minor importance.

Grass pollen is the greatest offender in Australia.<sup>6,20</sup> The season extends from September to December. Plantain rates second to the grasses as an offender and pollinates in practically the same months as the grasses. The trees pollinate in July and August, but are of slight importance since their pollinating periods are only of two to three weeks' duration.

In New Zealand<sup>14</sup> the grasses begin to pollinate near the end of November, reach a peak in January and terminate by the end of February. The trees pollinate from August through October, the highest pollen counts furnished by *Pinus insignis*, *Macrocarpa*, *Sycamore*, *Oak*, *Tutu*, and *Silver Birch*.

H. J. Hara<sup>13</sup> states that it is interesting to note that there have been no cases of pollinosis reported in Japan, although vegetation such as



grasses, lambs quarter and cereals is plentiful. The people of Japan have always been free from hay fever, although other allergies are as frequent as in other parts of the world.

Hay fever in most of the South Sea Islands is practically an unknown quantity. From Hawaii there is reported a perennial yield of grass pollen, algroba or kiawi tree pollen and some monkey pod tree pollen.

Gutmann,<sup>12</sup> in 1942, reported hay fever in Palestine. He found Bermuda grass of greatest importance being perennial in nature. He states that a special peculiarity of the country is the wide distribution of citrus plants. The "stupefying" odor of the blossoms in April and May in the vicinity of the orange groves occasionally forces even healthy persons to evacuate the vicinity for a time.

The cause of hay fever in South Africa<sup>21</sup> is also mainly Bermuda grass plus some of the tall veldt grasses (*Eragrostis plana*). The compositae are abundant and occasionally cause trouble as do the mimosa (*Acacia robusta*), lambs quarter (*Chenopodium album*) and the pepper tree (*Schinus molle*).

On the European mainland the most common offender is also grass. In Denmark<sup>2</sup> the pollination of grasses starts the first week of June, reaches a peak in the third week of June and ends in the last week of July. According to Landau and Gay,<sup>19</sup> the absence of ragweed is the outstanding feature in European hay fever. In Germany<sup>19</sup> allergy to linden accounts for 10 to 20 per cent of all hay fever cases. Allergy to hazelnut, willow and poplar is fairly common. The more important fungi in Germany are *Aspergillus fumigatus*, *Aspergillus niger*, *Penicillium glaucum*, rusts and smuts. The vast majority of hay fever cases however, result from grass sensitization. From Prague, in Czechoslovakia, Hlavacek and Blattney<sup>15</sup> report the grass season from the end of May to early in July.

Gay, Curtis and Norris<sup>9</sup> report that in Bermuda there is only one offending pollen of clinical importance, that being the cedar (*Juniperus bermudiana* L.). A cedar pollen sensitive patient suffers five weeks from late February to early April. Although grass and plantain are present, clinical observations of the inhabitants and visitors confirm the general opinion that grass pollen and plantain pollen hay fever is unknown or of no clinical significance. No ragweed is found in Bermuda.

In Brazil<sup>11</sup> there is only one hay fever season of clinical importance. It continues through the last two weeks in May and the first week in June. This pollen season is that of the grasses with Bermuda grass predominant.

From personal observation in North Africa, Italy and Sardinia, grasses are the most important causes of hay fever. This observation is confirmed by studies made by Kalisch in Italy and Weitz in North Africa. The main season occurs in the latter part of April and extends through June, although some cases are seen as late as the end of August or the beginning of September.

The main offenders of perennial rhinitis may be divided into two groups, first, the specific factors and second, the nonspecific factors with which the soldier comes in contact. The specific factors are mainly inhalants and consist of house, barracks and tent dusts, wool, cotton, feathers, tobacco, pyrethrum, soaps, toilet articles, straw dust, newspaper dust and sawdust. Other factors such as horse dander in the horse cavalry and animal danders in those outfits having animals as mascots are found in particular units. Flying personnel come in contact with rabbit and wool linings in their flying clothes, and kapok lining in certain types of planes. Kapok can be a factor on transports using life preservers made from this material. Occasional cases, with foods as specific etiological factors, are found.

Nonspecific factors such as sudden changes in temperature, irritating odors, vasomotor changes due to psychic causes, extremes in humidity, sudden changes in humidity, physical and mental exhaustion, and infections may be the aggravating cause of perennial rhinitis. In occasional cases some of these nonspecific factors may be the specific factor, viz., bacterial allergy and physical allergy.

The prodromal symptoms of allergic rhinitis consist of a feeling of weakness, depression and irritability. The patient frequently complains of vague disturbances of the eyes, nose, and ears, digestive sluggishness, drowsiness after meals and occasional localized or generalized itching. Symptoms may develop slowly or acutely; the former is more common in cases of perennial rhinitis while the latter is more common in cases of hay fever.

The patient has a distressing urge to sneeze, sneezing occurring in paroxysms of ten to fifty sneezes, and at times causing almost complete exhaustion and pain in the chest. Itching of the nose may be intense and is often accompanied by a burning or tickling sensation of the nose and the roof of the mouth. There is a rhinorrhea of a clear, watery fluid, at first containing only a few cells and later containing more cells and becoming mucoid. The secretion is usually nonirritating although the nose may become irritated from the mechanical effect of wiping. Nasal obstruction is common but not constant. It is due to the edema of the mucosa lining the turbinates. Patients frequently complain of nasal obstruction on the dependent side of the nose while lying down. Post-nasal drainage unassociated with anterior rhinorrhea is common in chronic cases of perennial rhinitis. Partial deafness may result from edema involving the eustachian tubes. These cases may present retraction of the ear drums and the patient may complain of earache. Frontal or antral headaches or a feeling of heaviness may result from mouth breathing produced by nasal obstruction. There may be some heaviness and constriction of the chest with or without dyspnea. These are warning signals of impending asthma. Approximately one-third of all patients with allergic rhinitis will develop asthma if allowed to go untreated.

Eye symptoms are very common in allergic rhinitis and consist of itching, sandy feeling of the lids, reddening of the conjunctiva, lacrimation and photophobia. Pain is not a constant finding; in fact it is found in a much smaller percentage of cases than one would expect upon noting the apparent pathology. The symptoms result usually from a conjunctivitis; however, keratitis<sup>4</sup> is not an uncommon finding; the ulcers are marginal, being about one to two millimeters from the limbus. At first they are discrete and usually involve just one quadrant, later they become larger, coalesce, involve the entire perimeter of the cornea, and finally result in a continuous marginal ulcer. A secondary central ulcerative keratitis may result from a lack of nutrition. Itching is intense and pain very mild. Iritis, uveitis, and retinitis have been noted.

Cutaneous manifestations are quite frequent. Generalized or localized pruritis will often usher in an attack of hay fever. Two cases of allergic rhinitis were seen whose main complaint was that of generalized itching with minimal nasal symptoms. Contact dermatitis due to pollen or other antigens is occasionally seen in conjunction with allergic rhinitis.

Systemic manifestations of weakness, lassitude and mental depression are frequently found. Fever is rare, anorexia and belching common.

In the early stages the nasal mucosa appears swollen and boggy, the color varies with the stage and duration of the process. It may be normal, slightly pale, markedly pale, bluish, pinkish, gray or red. In more advanced cases, there is thickening, hyperplasia and polypoid degeneration of the epithelium. Microscopically there is marked eosinophilic infiltration of the epithelial and the subepithelial structures, more advanced cases showing thickening, hyperplasia and polypoid degeneration of the epithelial layer with eosinophilic infiltration, edema, varying amounts of mononuclear, round cell, and lymphocytic infiltration and connective tissue proliferation. The blood vessels may be dilated, compressed or thickened, while bone may present either hyperplastic or atrophic processes. The periosteal layer shows round cell infiltration and connective tissue proliferation. Secondary infection modifies this picture.

The diagnosis of allergic rhinitis depends mainly on the history of recurrent bouts of sneezing, rhinorrhea and nasal obstruction. The diagnosis is confirmed by laboratory means including such procedures as eosinophile counts of the circulating blood, eosinophile studies of nasal and eye secretions, various types of skin tests, direct contact tests to the nasal mucosa and conjunctiva, passive transfer tests and dietary studies. This entire group of tests is seldom available to most military medical installations, especially overseas installations. Advanced front line installations have no, or at the very most, very limited laboratory facilities. Here the diagnosis must be tentatively made from the history and, at most, from the eosinophile count of the blood and secretions, and from the observation of the patient. Further to the rear, unless the hospital has an allergy section, the laboratory facilities will not include

specialized allergy tests. Most army allergy sections are inadequately supplied to do complete allergy studies. Again this is especially true of overseas installations. However, the vast majority of army allergy clinics are conducted by men especially interested in the military problems of allergy. These men, many of whom are well-trained allergists, are getting materials in many ways. It is difficult to do adequate dietary studies in most overseas hospitals because of the lack of foods and the absence of allergy kitchens.

The treatment of allergic rhinitis consists of elimination of the offending agent, hyposensitization and local treatment. Medical judgment as to the treatment of these cases, however, often differs in military therapy from civilian therapy. Elimination procedures are often difficult, if not actually impossible; hyposensitization routines can be impractical and local therapy may not be efficacious. In this paper only the military aspects of treatment will be discussed.

Forward echelons should evacuate cases of allergic rhinitis to the nearest allergy clinic in the rear echelon for study and disposition. The use of local measures such as ephedrine solutions or oils intranasally, inhalers of various types or oral preparations of ephedrine, atropine and sedatives will usually suffice to give the soldier relief until he is evacuated. On missions, men who suffer from allergic rhinitis can be dangerous to his fellow soldiers, such a case was seen by Capt. A. C. Kalisch, MC.<sup>18</sup> A mortar detachment was ordered to wipe out a gun position in one of the hills of Italy. These men proceeded to climb to an advantageous position, without giving themselves away to the enemy. As they were digging in, one of the members of the detachment began a bout of sneezing. The enemy then noting this new mortar position immediately trained machine gun fire on this little group and caused three casualties. Men with allergic rhinitis cannot be used where secrecy is paramount. This applies especially to reconnaissance troops of various sorts, litter bearers, snipers, troops on special missions, etc. It is our opinion that no case of allergic rhinitis should be in actual fighting positions because first, these men are not dependable, having periods of marked inefficiency due to sudden and often unpredictable bouts of sneezing and second, there are so many places where these men could serve a useful purpose that it is unnecessary to assume the risk and the treatment of these cases under such adverse conditions.

After the allergic case has been evacuated to an allergic section, it becomes necessary to decide what type of therapy and what disposition of the soldier should be made. This of course depends on where the patient is and what the local conditions are.

Seasonal hay fever due to trees uncomplicated by other clinical sensitivities need very little care except local therapy unless the symptoms are very severe, in which case hospitalization for the short time necessary for the cessation of his symptoms is recommended. Grass hay

fever cases offer a much more difficult problem because it must be remembered that these men are lying in the grass, sleeping in grass, and walking through grass so that there is very intimate contact with the offending agent. Thus, pollen counts will not reflect the actual conditions of pollen saturation encountered by the soldier. These men should be hyposensitized and reassigned. They should not do front line work regardless of the apparent degree of severity because mild cases can easily become severe under the very adverse conditions "up front." He need not be designated as limited duty but simply put in a rear echelon as general duty. The hyposensitization should be perennial because, during the fast movement of troops, the season may vary so as to leave him unprotected if only preseasonal measures are used. Parenteral treatment is at present more satisfactory than oral therapy; however, the limitations of oral therapy should be further studied and if possible, adjusted to military needs. Oral therapy would be of tremendous value in the treatment of allergic disease in the army.

Hay fever cases complicated by clinical perennial rhinitis or asthma should receive treatment for both conditions and be classified to limited duty. It is preferable to keep these men on duty within the continental limits of the United States.

Uncomplicated cases of perennial rhinitis should be placed only in rear echelons and never in "front line" positions and if complicated should be on limited type of duty within the United States.

Uncomplicated ragweed hay fever cases will do well overseas, but should not be designated for battle duty, because of the possibility of transfer of sensitivity to other antigenic substances with subsequent breakdown. Complicated ragweed cases should be kept within continental limits of the United States and, if feasible, sent to low ragweed pollen areas such as southern Florida or west of the Rocky Mountains. All cases of ragweed hay fever should receive perennial hyposensitization. It would be advantageous to have a copy of the treatment record accompany each man on troop movements to be delivered to the next station for continuation of therapy. It has been unsatisfactory to classify hay fever according to the degree of severity because such a classification depends on the personal opinion of the examiner and the history of the patient. The severity of hay fever is reflected in the history of the case in direct proportion to the anticipations and desires of the patient; if the examination is for a pleasant assignment the patient minimizes his symptoms, otherwise he exaggerates them. The severity of hay fever also depends on the pollen counts, intimacy of contact and various non-specific factors. We feel that no case of uncomplicated seasonal hay fever need be separated from the service.

The military treatment of soldiers in the United States does not offer the problems of overseas treatment. The prime object of an allergy section in the United States should be to prevent soldiers with allergic

conditions from getting to places where they will be a burden. It is absolutely essential that there be close co-operation between the medical and the personnel sections. These soldiers afflicted with the various allergies can do good work, but they cannot do it under all conditions. This fact must be recognized and proper emphasis placed upon it.

It has been the purpose of this article to bring to light more of the detailed problems of military allergy, especially the problem of allergic rhinitis and to try to offer in general, a workable solution. It is well recognized by the authors that in time of peace with a small standing army, the problem of allergy is minimized; but, during times of stress with the need of all available manpower, it becomes essential that we do not discard a group of men that are capable of performing useful, efficient work for the services. While the existence of allergic rhinitis has been recognized, the military attitude has been to shy away from this group of cases and to allow those men who are interested in delving into the problem of allergy to do so unofficially. Statistics of allergic cases in the army in previous wars are very unreliable because no definite mention is made of allergic rhinitis. The terms used at present, as found in the various extracts of regulations of sick and wounded, are hay fever, rose cold, polypus nasal, and rhinitis acute, atrophic, membranous and hypertrophic. From these diagnoses it would be extremely difficult to get a true evaluation of the statistical report of allergic rhinitis in the army. Thus the problem of allergic rhinitis finds only a tiny niche among the problems of the Surgeon General because statistically he has little on which to base official action.

#### SUMMARY

1. The incidence of allergic rhinitis at Fort Eustis, Virginia, was found to be 6.3 per thousand men.
2. Emphasis is placed on the differentiation between complicated and uncomplicated cases of allergic rhinitis.
3. A general outline is presented of the pollen conditions in the various parts of the world.
4. The military treatment and disposition of cases is suggested.

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## SEVERE LIGHT HYPERSENSITIVENESS CURED BY CHOLECYSTECTOMY

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and

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IT IS a fairly well-established fact that the treatment of a hepatopathy, a gastro-intestinal disease, an endocrine dysfunction, a focal infection, or an intoxication will prove to be beneficial in many cases of light hypersensitiveness. Such therapy is often followed by a complete cure or at least a temporary disappearance of the cutaneous disease caused by light. It is now generally believed that these results may be attributed to the fact that the formation of photosensitizing or photodynamic substances is more or less completely checked by the elimination of the underlying disturbance.

Thus, in a case of hydroa vacciniforme, Urbach and Bloech<sup>20</sup> observed that antiluetic therapy which improved the patient's syphilitic hepatitis resulted in a disappearance of the concurrent porphyria. Barber<sup>1</sup> described a patient who acquired light dermatitis by exposing himself to sunlight after overindulging in alcohol. His liver was greatly enlarged. A strict diet and complete abstinence from alcoholic beverages caused improvement of the liver condition and an early cure of the photosensitivity. Barber, Howitt and Knott<sup>2</sup> reported a number of cases in which treatment of a gastro-intestinal disease was followed by marked retrogression of skin manifestations produced by light. These authors expressed the opinion that the light hypersensitiveness was attributable to a bacterial toxin formed in the intestine. D'Amato<sup>5</sup> observed a woman whose skin lesions appeared only during her menstrual period. Following temporary inhibition of menstruation by roentgen irradiation, the patient's manifestations of light hypersensitiveness disappeared, but recurred some months later when menstruation returned. Lancaster<sup>7</sup> observed five cases in which the correction of menstrual disturbances, by the administration of estrogenic substances, was followed by a permanent restoration of tolerance to sunlight. Similar observations have been reported by Thurman<sup>17</sup>, Brunsting<sup>4</sup>, and also by one of us (E. U.).<sup>19</sup> Stokes and Callaway<sup>16</sup> have called attention to the development of sensitiveness to light in patients with either systemic or local infections. Sonck<sup>15</sup> reported a case of light hypersensitiveness in a patient suffering from lymphogranuloma inguinale; following a radical operation (extirpation of the rectum), the photosensitivity disappeared.

We wish to report a case in which the removal of the patient's diseased gall bladder was followed by the complete cure of a severe light dermatitis of nine years' duration.

From the Allergy Research Foundation, Inc., Philadelphia, Pa.

Mrs. M. W. L., sixty-three years of age, enjoyed perfect health up to the age of fifty-one years. In July, 1932, she noticed that her skin (face, neck, back of the hands) became unusually red after exposure to sunlight; and that this reddening disappeared when she stayed at home for a few days. The skin was found to be definitely more irritable at the seashore than in Philadelphia, and in the late fall the reddening ceased altogether. Thereafter, each year, this light dermatitis recurred in the spring and regressed in late fall. In May, 1940, the patient took a long automobile trip, which brought on very severe inflammation and swelling of the exposed skin areas.



Fig. 1. Appearance of patient two hours following twenty minutes of exposure to July sunlight.

For many years, the patient had been complaining of vague abdominal pains and distention. In addition, she had had occasional attacks of excruciating pains under the right costal rib which often radiated to the shoulder blades. These she had considered as attacks of acute indigestion. The patient also complained of poor bowel function.

Her weight had decreased 20 pounds during the three preceding years.

Physical examination revealed a co-operative, highly intelligent patient, anxious to get well. Mouth in good condition. Tonsils not infected. Heart not enlarged. No murmurs. Blood pressure: 134/80. Weight: 153 pounds.

There was redness and slight swelling of the face, of the upper chest, and back of the hands.

After the skin manifestations had disappeared, the left side of the patient's face and neck were deliberately exposed to twenty minutes of July sunlight. Two hours later, the exposed areas presented severe reddening and swelling (Fig. 1). The right side, which had been covered with zinc ointment, remained normal.

By means of special light filters, whose wave lengths were selected to permit the partial absorption of the short and long waves, as well as of the ultraviolet rays of the visible and invisible sun spectrum (Urbach)<sup>10</sup>, it was determined that the patient's skin was hypersensitive only to the ultraviolet rays.

The high degree of the patient's sensitivity to light was illustrated by her developing a mild but definite redness of the exposed skin three hours after a sixty-minute exposure (6:15 p.m.-7:15 p.m.) in the very late afternoon on a cloudy day. This redness was observable during the next twenty-four hours.



Examination of the abdomen revealed tenderness in the right upper and lower quadrants on slight palpation. The liver and spleen were not enlarged. Bile drainage showed a poor gall-bladder function and typical cholesterol crystals microscopically.

Microscopy of nonsurgical drainage bile has been very useful in the diagnosis of gallstones. The finding of both cholesterol crystals and calcium bilirubinate pigment has been found by one of us (H. S.)<sup>2,8,12</sup> to be pathognomonic of gallstones. Cholesterol crystals alone have been found when either stones or a strawberry gall bladder were present. Cholecystography confirmed the diagnosis of gallstones.

Liver function tests, keeping in mind their limitations, showed a normally functioning liver. The hippuric acid test gave a 75 per cent excretion in two hours after a 4 gram dose.<sup>9</sup> The bromsulphaline excretion test was normal. The vanden Bergh qualitative test was indirect, and the quantitative test showed 3/10 of a mgm. of bilirubin per 100 c.c. of blood. The fasting blood sugar was 103 mg. per cent.

The blood count showed a hypochromic, normocytic anemia (hemoglobin 72 per cent, red cell measurements at upper limit of normal). The sedimentation rate was normal. Basal metabolic rate: —12 per cent. Morning and evening specimens of urine were normal except for a faint trace of albumen in the evening specimen.

Gastric analysis: Fasting: free HCl 22, total acid 38. Sixty minutes after Ewald breakfast: free HCl 30, total acid 50. No bile or blood was present.

Fermentation studies of the stools failed to reveal any abnormal fermentative or putrefactive changes in the bowels. Benzidine test for blood in feces was negative.

Porphyrin study in feces: ether extract and HCl extract showed a marked fluorescence with ultraviolet light.

Dried smear of feces: Ratio of 3 to 1 of Gram-negative to Gram-positive organisms. Type of bacteria: Small Gram-negative organisms—some coccoid—some in short chains. Moderate number of Gram-positive cocci in pairs. A few large thick Gram-positive rods, single and short chains. A few large slender Gram-positive rods, single and in short chains. Fat: not present. Starch: negative. Muscle fibers: none noted. Numerous vegetable fibers.

Bacteriology: (a) Aërobic Blood agar plates showed the predominant organisms to be *Streptococcus viridans*. However, relatively few bacteria grew as compared with a normal fecal flora. Endo and Sabouraud plates show essentially the same findings.

(b) Anaërobic. Blood agar plates showed heavy growth chiefly bacteriodes, occasional *B. coli hemolyticus* and few indifferent streptococci. Deep meat culture showed marked digestion.

Stool cultures, therefore revealed a preponderance of *Streptococcus viridans* and a very scant growth of aërobic bacteria. On the other hand, the anaërobic flora was heavy with bacteriodes as the leading organisms. These findings indicate that the flora of the intestine was pathologic.

Twenty-four hour output of porphyrin in urine and stool after the patient had been on a meat-free diet showed a slight increase over normal of porphyrin in the stool and a normal output in the urine.

Since the usual dermatologic methods to protect the patient against light were ineffective and since medical management failed to control the gall-bladder condition, the gall bladder was removed on April 10, 1941, by Dr. William Bates. The gall bladder showed evidence of chronic disease, contained stones of the mixed type, and the gall-bladder wall was thickened. Gram-positive cocci were found in a stained smear of the bile but culture of the bile yielded no growth of organisms.

Four weeks after the removal of the gall bladder, the patient exposed herself

to sunlight. While her light sensitiveness showed very definite improvement, a slight rash did develop on her face, neck, and arms. However, three months later (July, 1941), the patient was able to sit in the sun without any abnormal skin reaction resulting. Since then, now nearly four years, there have been no recurrences of the skin rash despite frequent exposure to strong sunlight at the seashore. There have been no gastro-intestinal symptoms since the cholecystectomy. A recent twenty-four-hour stool and urine porphyrin determination yielded normal results.

#### DISCUSSION

In the introductory paragraph of this paper, a few examples were cited to demonstrate that light hypersensitiveness may be brought about by a great variety of conditions. Our understanding of the true nature of the mechanism involved is, as yet, sketchy at best. However, in a number of instances, there is good reason to believe that the primary disease brings on a porphyrinopathy, which, in turn, creates hypersensitiveness to light.

In our patient, an infected gall bladder was, in all probability, the primary cause of the actinic dermatitis. The literature contains reports<sup>6,12,14</sup> which show that cholecystitis may be the sole cause of certain skin diseases in which extirpation of the gall bladder was followed by a disappearance of the skin lesion.

Unfortunately, we are unable to present any data that would establish the mechanism by which the diseased gall bladder caused the skin sensitivity to light in our patient. Certain theoretical considerations are presented, therefore, with due regard for the breach in our evidence to support them.

The rapid and complete restoration to normal of the patient's skin reaction to light after cholecystectomy naturally offers the removal of a focus of infection as a possible explanation for the result. The removal of such a focus, if it were a source of some sensitizing agent for the patient's skin, could result in a cure.

Another possibility might be considered. A twenty-four-hour stool and urine output of porphyrin did show a slightly increased amount over normal in the stool but no alteration from normal in the urine. Recent investigations in light dermatoses have shown the porphyrin content of the feces to be increased in the presence of certain pathologic intestinal flora, notably with a preponderance of streptococci over *Bacterium coli* (Urbach).<sup>18</sup> It is noteworthy that, in these cases, an increased porphyrin content will be found only in the stool, but not in the urine and blood. The porphyrins that are absorbed in the intestinal tract ultimately reach the liver by way of the portal system. Here the porphyrins are, in part, broken down or otherwise transformed; most of them, however, are returned to the intestinal tract in the bile (enterohepatic circulation of the porphyrins).<sup>21</sup> But if the mucous membrane of the gall bladder is irritated, it is conceivable that the increased amounts of intestinal porphyrins brought to the liver may be resorbed from the

bile through the inflamed mucous linings of the gall bladder, and so reach the general circulation in abnormal amounts, which, in turn, may eventually cause skin sensitization to light. A parallel for such activity by the gall bladder with respect to porphyrins may possibly be found in the concentration of bile salts in the bile by the normal gall bladder<sup>10</sup> and in the disappearance of bile salts from the contents of the diseased gall bladder.<sup>11</sup>

#### SUMMARY

A case of severe light dermatosis which was cured by extirpation of the infected gall bladder is reported.

As in other cases of light hypersensitiveness, a pathologic intestinal flora was found. This may well have been the cause of the increased porphyrin content of the stool.

Two possible mechanisms are suggested, through either of which the diseased gall bladder could have been responsible for the sensitizing agent causing the light hypersensitiveness. These would also explain the rapid and apparently permanent clinical recovery from this hypersensitiveness as a result of the cholecystectomy.

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# Editorial

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## STANDARDIZATION OF EXTRACTS

For years the standardization of extracts has been a debatable topic. Numerous methods of extraction and standardization have been used when making allergenic extracts for diagnostic and treatment purposes. The various commercial manufacturers of allergenic extracts as well as clinical allergists making their own extracts have been blissfully going along compiling statistics, none of which is comparable or uniform.

The Standardization Committee of the American College of Allergists was organized for the establishment of standards for allergenic extracts, and it is making progress despite the many handicaps of a global war. The Committee is primarily interested in investigations which may give a clue to the real nature of allergens, as this information is necessary if logical and practical methods of standardization are to be developed. The solution of this problem will mean far more than the mere "purification" of an allergen, laudable as that may be. In most instances the chemical nature of the allergens responsible for clinical symptoms is not known. In the case of ragweed we have been led to believe that aqueous extracts of allergens are proteins whose antigenicity depends on their nitrogen content, although it is now shown that the active antigens in ragweed pollen are not proteins but actually are a flavone-polypeptide-carbohydrate complex. Finally, it is probable that satisfactory methods of standardization will include both a chemical and biological assay of the allergen.

The progress of the Committee is evidenced in several ways:

1. Through the efforts of Dr. George E. Rockwell, Chairman of the Committee, a research fellowship paying \$1,500 a year to continue for two years, has been placed under the direction of Professor M. A. Logan, Department of Biological Chemistry, University of Cincinnati Medical School.

2. It is hoped that the work which will result from the fellowship placed under the direction of Dr. Charles F. Code of the Mayo Foundation (announced in the *ANNALS OF ALLERGY*, November-December, 1944), may among other things give additional information as to the action of allergens.

3. The Committee has the unselfish and wholehearted co-operation of a number of members of the College, some of whom are on the scientific staffs of pharmaceutical concerns making allergenic extracts. The College is fortunate in having allergists of international reputation working with the Committee and devoting much of their time to the subject of standardization of extracts.

4. The College has the assurance of Dr. M. V. Veldee, Chief of the Biologics Control Laboratory of the United States Public Health Service,

of their co-operation in our endeavor to establish standards for allergenic extracts.

5. The Committee is actively working on the standardization of dust and pollen extracts, and we have every reason to believe that they have already made some very important advances along these lines. Out of this work, specifications should come which if met will give the assurance of uniform and comparable extracts.\*

When considering the importance of this subject, we plead to all allergists, who appreciate the great need for a satisfactory method of standardization of extracts, to co-operate with us in this endeavor.

STANDARDIZATION COMMITTEE

## EDUCATION IN ALLERGY

The Educational Committee of the College† is initiating an intensive, earnest, and vigorous program of undergraduate education in allergy. After a study of the different facilities offered in allergy education by the leading medical schools for both graduate and undergraduate students, it is plainly evident that the rapidly increasing importance of allergy in relationship to various diseases is not appreciated by the majority of teaching faculties. There is a failure in the teaching of physicians to apply allergy properly to their practice whether general or specialty. Many medical schools do not include the teaching of allergy at all, while others offer a few lectures and others have a very limited didactic and clinical course integrated with the department of internal medicine.

With these facts in mind, the Committee realized the enormous task confronting it. Obstacles are numerous. Many allergists who have had certification in medicine handed to them by virtue of their age, influence or past accomplishments feel that the teaching of allergy should be relegated entirely to the department of internal medicine.

Before discussing this phase, let us review evident conditions which are going to influence graduate education in the future. There are now fifteen specialty boards that have certified a total of more than 24,000 physicians. According to Dr. Victor Johnson, Secretary of the AMA Council on Medical Education and Hospitals, these specialty boards have about attained their maximum number. Specialists in tuberculosis, cardiology, allergy and gastro-enterology are certified by the American Board of Internal Medicine. The various boards have a ruling requiring a diplomate to limit his work to one specialty which has already resulted in specialists, who practice in small cities, where there are too few patients seeking a specialist's care, to complain about this limitation.

There is an increasing tendency to seek board certification, as shown by a survey made by the AMA Committee on Postwar Medical Service. Approximately three-fourths of Army physicians indicated that they were

†The names of the members of this Committee appear on the officers' page of this issue.  
\*In the May-June issue there will be an important announcement concerning standardization.

already certified by one of the specialty boards, or were planning to take the examinations for them on resuming civilian practice. The Army and Navy, government agencies, medical schools and insurance companies are all emphasizing certification, so that those who are not diplomates are becoming increasingly apprehensive lest they find themselves at a disadvantage in postwar practice. Inspiring further increased certification is the fact that many county medical societies have urged board approval, believing that certification is a guide to the laymen and general practitioner when indicating the difference between the competent specialist and the man who claims to be one.

With time and distance becoming a negligible factor, the family physician is rapidly being replaced by many strategically located hospitals in smaller cities that have every facility and competent specialists.

The laudable program for raising medical educational standards by the Council on Medical Education and Hospitals is going to produce a demand in graduate education requiring increased teaching material and staffs, leading to certification, so that the supply is only going to be met by the increase in specialists.

These are imminent problems which the Council will have to solve by modifying their present restricted view limiting the establishment of separate boards for specialists in tuberculosis, cardiology, allergy and gastro-enterology or face the possibility of specialists in these fields setting up their own specialty boards. Any discrimination against such newly organized groups becomes a restraint of trade.

Since allergy now embraces about fifteen diseases, and some of the most important come under specialties entirely apart from internal medicine, allergy should be considered a specialty which must be correlated with every other specialty of medicine. With this policy, the College has been able to secure the hearty co-operation of some of the most outstanding specialists in other fields who are properly applying allergy to their practice or teaching it in medical schools. These include pediatricians, otolaryngologists, dermatologists, gastro-enterologists, immunologists and bacteriologists. These men are certified by their various specialty boards and have gone through all the disciplines of medicine required by an accredited medical school. Limiting the teaching of allergy to either medicine or pediatrics was a very narrow view which retarded allergy education before the College was organized. In whatever field allergy exists, undergraduate students and graduate students should be taught concerning it. It is well known that many internists doing allergy take care of allergic infants and most of them, who have no special pediatric training, do this very poorly, causing great discredit to allergy. This rightfully applies to every other specialty in which allergy is encountered in its daily practice. When establishing a broad teaching program, it therefore seems logical that the heads of the departments of dermatology, gastro-enterology, pediatrics, otolaryngology, et cetera, be sufficiently trained in the practice of allergy so that they

may adequately teach the undergraduate student how to apply allergy procedures to his patients or specialty so that when he graduates, whether he chooses the specialty of allergy or not, he will be far better fitted to apply it to his practice as a result of receiving this type of special training, and if he desires graduate training in allergy, he will already have a good foundation.

The heads of these departments should be integrated under a committee representing these various specialties and not just under internal medicine.

With these problems in mind, the Educational Committee is arranging a practical and efficient, specific curriculum of what they consider to be minimum requirements for the teaching of allergy. Increased clinical facilities will be stressed, and not lectures.

The theme of this program is to have allergy considered as an integral part of each of the allied fields or specialties.

When the allergist has a problem that requires the consideration of one of the allied specialties, it is absolutely necessary that there be a common denominator or mutual ground of understanding or appreciation. These allergy problems can best be solved or managed by wholehearted co-operation and united approach, if allergy is to advance and results are to be more efficient.

F. W. W.

*The Effect of the Injection of Histamine into the Brachial Artery on the Permeability of the Capillaries of the Forearm and Hand.* Stead, E. A., Jr., and Warren, J. W.: J. Clin. Invest., 23:233, 1944.

Injuries to the forearm and hand make the capillaries more permeable. The authors use a rise in hematocrit reading without a corresponding rise in the protein concentration as an indication that protein was escaping from the capillaries. 0.15 mm. of histamine was injected into the right brachial artery and, for several minutes after this injection, samples of blood were withdrawn. The subjects complained of pain, swelling and stiffness in the hand and forearm, with this reaction being confined to the extremity used. The hematocrit reading and the hemoglobin concentration of the forearm blood increased but the protein concentration showed little change. Arterial occlusion, by a blood pressure cuff, showed a tendency for an increase in both the hematocrit reading and protein concentration. A reaction similar to that produced by histamine is not seen in uninjured tissue in the usual types of shock.

*The Influence of Certain Amino-acids on Histamine Reactions and Anaphylactic Reactions in Intestinal Strips of Guinea Pigs and in Intact Guinea Pigs.* Landau, S. W., and Gay, L. N.: Bull. Johns Hopkins Hosp., 74:55, 1944.

The authors used arginine monohydrochloride and histidine monohydrochloride in the successful prevention of the effect of histamine and/or antigen on the intestinal strip of guinea pigs. The action of acetylcholine was not suppressed by these amino acids. Death from histamine injection can be prevented in guinea pigs by the previous protection afforded by arginine; but this substance did not protect against death in anaphylactic shock in similar doses. Arginine was found to be highly toxic in high dosages. Skin reactions were not affected by the use of 2 per cent arginine.

L. J. H.

# Progress in Allergy

## ANNUAL CRITICAL REVIEW OF THE RECENT LITERATURE ON BRONCHIAL ASTHMA

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The previous survey of the literature included a study of most of the articles on bronchial asthma up to about October, 1943.<sup>104</sup> The present review covers the period from October, 1943, to the end of December, 1944, but also mentions a few foreign papers which did not become accessible until recently.

Many articles continue to appear, many of which are merely reviews. New data has appeared on the military aspects of allergy, and some important, even sensational, work has been carried out in the condition now known as "Tropical Eosinophilia."

### TROPICAL EOSINOPHILIA AND LOEFFLER'S SYNDROME

Within very recent years an apparently new condition has been discovered which Weingarten<sup>109</sup> has labelled "Tropical Eosinophilia." The condition usually begins insidiously, with malaise, low-grade fever, and headache. This period lasts about a week and usually leaves the patient weak and listless. An unproductive cough follows after a period of a few days to several months, and wheezing and dyspnea are often associated. Patients state that they have "asthma." The spleen becomes palpable, and x-ray films of the chest usually show a fine mottling of bronchopneumonia type in both lungs. Unless treated specifically with arsenicals, the condition may become chronic. No fatalities have occurred.

Leukocytosis (up to 60,000) and marked blood eosinophilia (up to 89 per cent) are striking features. A lesser degree of eosinophilia is also found in the sputum.

Tropical eosinophilia has become frequent among both civilians and soldiers in the Bombay region of India. It has also been found on the seaboard of Malabar, Coromandal, Gujarat, and Kathiawar. There is some doubt of its existence in other tropical regions, e.g., Porto Rico. It has been found in soldiers and civilians returning from the tropics, and therefore it is important that we recognize it. This is all the more necessary because one to six intravenous injections of such arsenical preparations as neoarsphenamine or novarsenobillon (N.A.B.) are specific. The symptoms abate at once, and the leukocytosis and eosinophilia disappear. Recurrences can occur. Oral administration of arsenicals, e.g., carbarsone, has also been effective.<sup>29</sup>

The fact that arsenicals cure the condition suggests that the disease is due to spirochetes or to protozoa, but search for these has so far been unsuccessful. All tests for parasites in the blood, urine, stools and sputum have been negative. Credit for the brilliant results obtained in tropical eosinophilia go to Weingarten<sup>109</sup>, Heilig and Visveswar<sup>50</sup>, Owen<sup>72</sup>, Vaidya<sup>107</sup>, Emerson<sup>29</sup>, and Apley and Grant.<sup>3</sup> Fenner<sup>32</sup>, from Australia, describes a case of "eosinophilic leukemia and asthma"—the fact that this soldier had an enlarged spleen and 60,000 leukocytes, with 74 per cent eosinophiles, would suggest the diagnosis of tropical eosinophilia. It would be interesting to see if injections of arsenicals would cure the patient. Unless there are definite contraindications, it would seem logical to try arsenicals in the treatment of asthmatic patients who have a very high blood eosinophilia.

In the differential diagnosis of tropical eosinophilia, one must consider worm infestations, Loeffler's syndrome, Hodgkin's disease, malignancy, and allergic bronchial



asthma. In worm infestations the cause is usually found sooner or later. In trichiniasis the fever is apt to be higher at first, and ova can usually be found in the stool and the worm in the muscles; arsenic is of no help. Hodgkin's disease rarely has such a high percentage of eosinophiles and seldom more than 10,000 white cells. True allergic bronchial asthma likewise rarely, if ever, displays marked leukocytosis with high eosinophilia; fever is not characteristic, and enlargement of the spleen is not present. The wheezing in asthma is usually higher pitched.

Loeffler's syndrome has a transient but more solid infiltration of the lungs as shown by x-ray films; white cells are usually up to about 15,000, and eosinophilia is marked. The consolidation usually clears in three to eight days. Hansen-Pruss and Goodman<sup>45</sup> report migratory pulmonary consolidation occurring in six allergic individuals. They prefer the term "allergic pulmonary consolidation" to "Loeffler's syndrome." In their cases, the eosinophilia persisted after the asthma and x-ray evidence of consolidation had disappeared. Sulfonamides were of no benefit. No fatalities have been reported. Jones and Souders<sup>56</sup> made fluoroscopic examinations of the chest of 6,283 discharged soldiers; abnormalities were found in fifty-five cases, thirteen of which were diagnosed as Loeffler's syndrome. Pirkle and Davin's patient<sup>75</sup> showed consolidations which continued to migrate for eight months. Lowe's paper<sup>64</sup> deals with eosinophilia found in servicemen who have become worm-infested while in the tropics.

## MILITARY ASPECTS

All medical officers agree that asthmatic individuals do poorly in the Service. They urge civilian physicians to send notes to the induction boards to keep their asthmatic patients out of the Service. Gold and Bazemore<sup>39</sup>, from Camp Blanding, Florida, have made special allergy studies prior to induction on all individuals with a history of allergy. The local induction station referred 143 persons who gave a history of asthma. Of these, 132 were diagnosed bronchial asthma, and 42.4 per cent were recommended to be rejected from military service. It is much better to reject these men at once than to force them from their civilian pursuits, as most will develop more attacks of asthma in the Service, be hospitalized and finally discharged. Edwards<sup>28</sup>, from the Letterman General Hospital, San Francisco, California, has attempted to prove the presence or absence of allergy in selectees and in candidates for commissions. He makes scratch tests first, then intracutaneous, if necessary. He uses extracts of mixed trees, grasses, fall pollens, timothy, ragweeds, epidermals, some inhalants (flaxseed, cottonseed, pyrethrum, and orris root), mold mixtures, and house dust. He omits food tests as unreliable in many cases and therefore unsuitable for mass testing. This procedure is a step in the right direction.

Although patients with asthma of any but the mildest degree are not supposed to be in the armed forces, the fact is that thousands of them are in the Service, are taking up hospital beds, are receiving care in clinics, and are being discharged, some with pensions. During 1942, Gold and Bazemore<sup>39</sup> report that 399 allergic patients were admitted to their hospital and 911 to their outpatient clinic. Bronchial asthma was the diagnosis in 51 per cent of the cases, a rate of 4.8 per 1,000 soldiers. Of those hospitalized, 24 per cent of the asthmatic patients were discharged from service, 58 per cent returned to full duty, the rest to limited duty. It is interesting to note that 65 per cent of those discharged had less than six months' service prior to discharge, and 21 per cent had less than thirty days of service.

Alford<sup>2</sup>, from the Percy Jones Hospital, Battle Creek, Michigan, summarized his first 100 cases of asthma in soldiers, and concludes:

1. Men with active bronchial asthma should not be inducted.
2. Soldiers with bronchial asthma may be placed on nonstrenuous duty if:
  - (a) their attacks are due to a single sensitivity for which rapid, adequate treatment is available

- (b) attacks are mild and infrequent, not preventing light duties
- (c) the initial attack occurred overseas
- (d) the attack in the Army was the first one since childhood.

Alford also found that in soldiers whose first attack occurred overseas, a positive family history was only found in 21 per cent, as compared to 65 per cent in those whose asthma was present since childhood. Alford also made skin tests with extracts prepared from dust secured from barracks bags which had been overseas and found the nitrogen content of overseas dust was twenty times as strong as his stock United States dust. One patient had a severe attack of asthma after 0.10 c.c. of this overseas dust extract, and asthma was also induced by inhalation. Molds, dust, and dampness seem to be the important factors, especially in the South Pacific.

Hampton and Rand<sup>43</sup> report from the Allergy Section and Clinic, A.A.F. Regional Hospital, San Antonio, Texas, Aviation Cadet Center, from August 1, 1943, to August 1, 1944. During the year, 8,409 visits were made by Air Force personnel to the Allergy-Clinic. There were 1,541 new patients, of whom 921 had respiratory allergy (hay fever, vasomotor rhinitis and asthma). Of 1,191 men who were discharged from service, 106 (8.9 per cent) had allergic diseases; eighty-six of these had bronchial asthma. Respiratory infections, both acute and chronic, were frequent and important complications, and occurred in 191 of 286 cases of asthma.

French and Halpin<sup>37</sup>, from the Fourth Service Command, Atlanta, Georgia, continue their reports, but, unfortunately, their team has been dissolved. They gave four courses of instruction to 180 medical officers, and they treated 32,046 allergic soldiers. They used standardized allergenic extracts prepared by their own laboratory; manufacture of these extracts has been discontinued. They supervised eighty-nine allergy clinics in this command. French and Halpin report as follows: 9,591 cases of bronchial asthma, of which 946 were seasonal; 1,384 were associated with hay fever, and 7,261 were perennial. Asthmatic soldiers occupied many of the hospital beds, 5,447 of a total of 8,139 beds filled by allergic individuals, including sufferers from poison ivy. The Certificate of Disability Discharge was given to 3,231 asthmatic soldiers.

Discussing this paper, Leider<sup>62</sup> gives 1943 statistics from the Walter Reed Hospital. Asthma occurred in both white and colored patients, and both "extrinsic" and "intrinsic" cases occurred. Asthma occurred prior to military service in 75 per cent of the cases, and during military service in 25 per cent. There were 186 asthmatic soldiers; of these, twenty-nine (15 per cent) had their first attack overseas, fifteen in Porto Rico and seven in Panama. Another 71, when overseas, had exacerbations of pre-existing asthma; in this group, England, with twenty-four cases and with a damp climate, led all other countries. Dampness is a definite factor in England and in the tropics. After these overseas asthmatic soldiers returned to the zone of the interior, forty-two of the 100 remained free from asthma, thirty-five had mild and twenty-one moderate symptoms, and two had severe attacks. Of the total 186 cases, ninety-one were returned to limited duty and ninety-four were discharged from the Service.

Shahon<sup>91</sup> discusses the difficulties encountered by the induction board physician. He points out:

1. If the examiner's physical examination of the soldier is negative, there is no history of allergy in the soldier or in his family, and skin tests, if done, are also negative, then allergic disease was not present at the time of induction. If this soldier should later develop an allergic disease, the condition has developed during service, and if discharged he is entitled to full benefits. It is possible that factors like overexertion, worry, exposure to excessive cold or heat, emotional strain, et cetera, may precipitate symptoms.

2. If the allergic condition was mild at the time of induction and later became so severe as to cause separation from the Service, the disease was undoubtedly aggravated by service. As regards rating for pensions, Shahon points out that, as

with other conditions, allergic diseases are rated in terms of severity. For example, asthma is rated:

- (a) asthma, mild—symptoms in attacks at widely separated intervals; no complications. Rating 0 or no per cent.
- (b) asthma, moderate—symptoms rather frequent (ten to fourteen-day intervals), with slight to moderate emphysema, with moderate dyspnea between attacks. Rating 30 per cent.
- (c) asthma, severe—frequent attacks, with moderate to severe dyspnea with emphysema, and also if heart action embarrassed. Rating 50 per cent.
- (d) If, with above symptoms, soldier also has dyspnea at rest with cyanosis and total disability. Rating 100 per cent.

## ETIOLOGY OF ASTHMA

Allergy to molds again is a subject for discussion. Despite many earnest studies, it is still apparent that there are some who are over-enthusiastic about the role of molds in causing asthma and rhinitis, and that others believe that molds are of little importance. The majority of investigators, however, know that molds are important, but we are still groping in many aspects of the question. Those who rely on scratch tests are convinced (this author is among this group) that positive scratch tests plus a good history for mold etiology means clinical allergy to these molds. But reliance on positive intradermal tests for molds is not nearly as accurate. This is shown by the somewhat pessimistic attitude of Prince, Morrow, and their coworkers who realize that they have lost a good part of the antigenicity in their method of preparing mold extracts. Realizing this, they are earnestly correcting their technique. Prince and Morrow<sup>80</sup> describe their methods of preparing mold extracts. Both spores and mycelia of *alternaria* and *aspergilli* are thoroughly broken up by the ball mill process. Defatting is not important. Prince<sup>79</sup> tested nine normal individuals with extracts of *alternaria* as well as with saline washings from pellicles and the broth from which the pellicles are grown, and found that these caused no skin irritation. But when pellicles in saline solution are washed prior to extraction, some of the positive-skin-testing quality is lost, as shown by tests on *alternaria*-sensitive patients.

Zink<sup>113</sup>, in another study in this series, concludes that:

1. Air-borne molds are clinically important in 25.5 per cent of 705 tested patients
2. *Alternaria* are the most important molds, with *helminthosporium* and *hormodendrum* lesser factors
3. *Aspergilli* and *penicillia* are of little clinical importance

Selle<sup>80</sup> was unable to demonstrate histamine or a histamine-like substance in the washings of *Aspergillus niger* or *Alternaria tenuis*, or in the broth on which these molds were cultured. Nor could he detect histamine-like substances in concentrated extracts of these molds which were used for skin tests. Figley and his co-workers<sup>85</sup> made intracutaneous tests on fifteen patients with clinical respiratory allergy to *Alternaria tenuis*. There were twenty-four control patients. *Aspergillus niger* was also tested. They found that the experimental extracts were about as active as extracts of the same fungi prepared by the usual methods; variations in technique of preparation were not important. Passarelli and his associates<sup>73</sup> have shown that molds are important allergens in Rio de Janeiro. Studies made from May 11 to September 4, 1943, revealed that the most common molds are *penicillium*, *hormodendrum*, and *aspergillus*; *alternaria* were rarely found.

New allergens have been reported. Oliveira Lima<sup>63</sup> described a patient with a positive family history of allergy who developed rhinitis and asthma five months after beginning the regular use of an insect powder containing timbó. Contact dermatitis developed at the same time. Timbó (*Lonchocarpus*) and Derris (*cubé*) are both plants of the *Leguminosae* family and are used as insecticides. In this patient,

scratch and passive transfer tests were positive for both plants. Patch tests were positive with the resinous constituents of timbó. Incomplete animal experiments indicate some cross reaction between the two plants. Sterling and Hollander<sup>95</sup> discuss a woman whose home, especially her bedroom, contained a great number of plants, and who suffered from bronchial asthma for fifteen years. Tests for the usual allergens were negative, but she gave two plus reactions to the following molds found in the soil: *helminthosporium*, *rhizopus*, and *aspergillus flavus* and *nidulans*. When the plants were removed from her house, she improved remarkably. Re-exposure to the plants was followed by asthma. Skin tests were strongly positive both for extracts made from the leaves of an *Aspidistra* plant and from the soil of the plant which contained hyperhumus fertilizer. Passive transfer tests were doubtful. Injections of both extracts have been given, and the patient has been symptom-free.

Cotter's patient<sup>21</sup> was shown to be allergic to aluminum dust which he inhaled when he bored holes into aluminum plates. Recovery followed removal from this dust, and exposure again brought on asthma. No skin tests were made. Toomey and Petersilge<sup>102</sup> describe a type of noninfectious dust bronchitis previously observed in the Dust Bowl area; similar symptoms occurred in institutionalized children who inhaled finely pulverized dust from a nearby playground. To complicate an already overcomplicated situation, Hooker<sup>53</sup> has shown that there is a qualitative difference among dog danders, depending on the breed of the dog. Cross-neutralization occurs between some breeds but not between others. It is therefore almost impossible to obtain a representative multivalent extract of dog dander. This may explain why skin reactions to dog hair extracts are almost always weaker than extracts of cat hair or horse dander. We should test patients with extracts made from the dander of their own dogs as well as with mixed dog hair extract.

Foods also cause symptoms, and Rinkel<sup>87</sup> states that the following events indicate that foods are the cause of asthma:

1. Production of large quantities of mucus
2. Acute attacks lasting two to five days, without essential changes in environmental factors
3. With the same environment, the occurrence of acute attacks in the middle of one night a week
4. Asthma only in the mornings and up to noon, then none the rest of the day
5. Asthma occurring each day about 4:00 to 5:30 P.M., not related to, or affected by, other inhalant or environmental factors.

This is typical, says Rinkel, of a food eaten both at breakfast and lunch. Nasal symptoms may accompany or replace asthma. Horesh<sup>54</sup> reports the case of a child who developed severe asthma both from eating cooked white potatoes and from the odor of potato, cooked or raw. Cooking odors are fairly frequent causes of asthma and rhinitis. Scratch tests were positive for potato and other foods and inhalants. Coca<sup>17</sup> again discusses his theory of "nonreaginic food allergy," as determined by an increase in pulse rate. This work may be important but needs confirmation.

A number of articles on miscellaneous causes of asthma have appeared. Thus Earle<sup>27</sup> describes the case of a sailor from the British West Indies who developed his first and only attack on board ship; the asthma disappeared when he vomited material containing three live *ascaris* worms. The stools were negative for parasites, and the personal and family history were negative for allergy. Skin tests, both scratch and intradermal, were positive for an aqueous extract of preserved *ascaris*. No further workup was possible, and, unfortunately, the sailor was killed in action a month later.

Another case of sensitization to thiamine hydrochloride comes from Stein and Morgenstern.<sup>94</sup> Their patient, addicted to the use of alcohol, previously had injections of thiamine. The latest series was given at regular intervals, and each

was followed by severe local pruritus and urticaria. Fifteen minutes after the eighth injection, generalized pruritus developed, together with asthma, shock and coma. Gradual improvement followed the administration of epinephrin and caffeine, although asthma persisted. Intracutaneous tests with thiamine led to a wheal and itching which persisted for six hours. Passive transfer was not done.

An important article comes from Randolph and Rawling.<sup>86</sup> Status asthmaticus developed in a patient on the seventh day of the nasal use of a solution containing sulfathiazole. Personal and family history were negative for allergy. One week after this patient was symptom free, a trial feeding of sulfathiazole caused a typical paroxysm of asthma, together with decreased vital capacity. Another patient, already allergic as shown by the history of atopic dermatitis, asthma and allergic rhinitis, developed asthma after the first dose of a second course of sulfathiazole treatment. In both cases, there was an increase in the percentage of eosinophiles in the blood in twenty-four to forty-eight hours after the sulfathiazole was given.

An interesting article from Deissler<sup>24</sup> would become practical only if gas warfare is resumed. He points out that any sort of respiratory irritant, e.g., various fumes, chemicals and smokes, tends to incite or aggravate attacks of asthma. Poison gases are especially potent in this regard. Therefore, an asthmatic patient should have priority in obtaining a gas mask. He should also:

1. Try on his mask frequently to eliminate psychic factors
2. Take epinephrin or epinephrin in oil and some ephedrin at the onset of the gas attack
3. Wear an identifying tag specifying that he has asthma, and, if necessary, that he should receive aminophyllin or epinephrin but no morphine or other opiates
4. He must not inhale 1:100 epinephrin during an attack for fear of inhaling the poison gas.

These precautionary measures may seem absurd, but as one who has gone through "gas" attacks and has worn a gas mask, they may become important.

Two papers concern the relationship of asthma and the weather. Feige and Rosenbaum<sup>31</sup>, from Tel-Aviv, Palestine, made meteorologic studies on three isolated dates when many children with chronic asthma developed severe attacks. There were no special changes in weather conditions on these three dates, although the authors point out that the asthma may have been due to sudden appearance of pollens in the air. Petersen and Vaughn<sup>74</sup>, in a scholarly exposition, conclude that "The inference is obvious that the clinician, while properly interested in the allergic background of the clinical symptoms, should by no means neglect the other environmental forces which are of significance not only for the allergic patient but for other individuals as well. Recognition of the basic organic rhythm, with its periods of increased or decreased susceptibility to attack, should, under all conditions, prove useful in the evaluation of the symptoms and therapy, as well as the prognosis." They strongly support Hilding's view<sup>51</sup> that, as a result of the local changes in the smaller bronchi, the ciliary action is lost, and the difficulty of removal of secretion is aggravated because the mucus remains attached over large areas to the cells which produce it, thus anchoring the mass to the wall. When the air passages have become sufficiently filled, the patient dies of asphyxia.

Psychosomatic allergy continues to draw attention. Mayer<sup>66</sup> believes that asthma is not a disease but a symptom-complex, and may be due to many causes; e.g. allergy, heart disease or any other cause of bronchial obstruction. His patient had several attacks of asthma which were precipitated by psychic stimuli, and the author therefore diagnosed the condition as "psychogenic asthma" and says the psychosomatic approach offers the best results in the treatment of asthma. (This paper, to me, is very poor, as it sees only the psychic aspects of asthma which we all grant are important but which are of little importance when the exciting organic cause, e.g., dog hair or egg white, is avoided). Another almost absurd article comes

from a nurse, S. Lane<sup>59</sup>, who writes about her own asthma. She accuses physicians: "I have never heard one of them mention the possibility of emotional factors causing asthma. They always seem to think that it can arise only on an organic basis." She discusses her own emotions as regards asthma; she has crying spells which she believes are substitutes for asthmatic attacks.

Brown and Goitein<sup>18</sup> state that "most investigators are agreed that a complex series of factors are involved in the perpetuation of the disorder and the initiation of accentuation and amelioration of attacks." They believe that sex is closely related to allergy and state that "sensitvity is displaced repressed sexuality." (It is hard to believe this; how can sex operate, for example, in a child whose asthma begins in infancy?)

Rubin and Moses<sup>88</sup> studied fifty-four asthmatic males by electroencephalograms and personality data. The former indicate a definite relationship between bronchial asthma and a dominant alpha record, i.e., about three times as many dominant alpha records were found in asthmatic as in normal persons. Dominant alpha records have been correlated with passive receptive type of persons. The author's own personality data indicate, in general, that there is a single family definite personality constellation. Asthmatic patients are fundamentally in the passive dependent group, and are children of overprotective dominating mothers. They have not cared for, striven for, or gained any marked degree of independence in life, and they continue to seek care and protection from their environments. Zeller and Edlin<sup>112</sup> studied 372 insane individuals by means of skin tests, histories from relatives and friends, and by watching for allergic symptoms, e.g., hay fever. By this systematic allergy survey, they proved that there is just as much allergic disease in the insane as in the sane. The reason one does not find symptoms in the insane is that he does not complain. Only the severe instances of allergy come to the attention of the medical attendants. This paper is in direct opposition to that of Leavitt<sup>61</sup>, who studied (but not by skin tests, merely by complaints of the patients and the observations of the medical staff) 11,647 patients afflicted by functional psychoses. He found only ten cases of bronchial asthma in this group, an incidence only about 5 per cent of that found in the general population. Leavitt did not find a single case of asthma in 5,000 mental defective and epileptic inmates of a state institution.

#### PATHOLOGY OF ASTHMA

Four papers on the pathological aspects of asthma need comment. Rackemann<sup>81</sup> discussing death from asthma, concludes that death is due to the development of obstructing plugs of tough, sticky mucus. The "typical" asthmatic lung was present in twenty-seven of his fifty cases in which death was due to asthma itself: voluminous distended lungs of bluish gray color; cut section reveals that the bronchi, especially those of medium or small size, are partially or completely occluded by plugs. He reports 55 other cases in the literature in which the "typical" asthmatic lungs were found, i.e., cases in which the clinical history and the mode of death are characteristic of bronchial asthma, in which autopsy reveals voluminous lungs and bronchial plugs, and in which there was no gross evidence of any other cause of death. In Rackemann's series, a total of 82 patients died because of asthma; most deaths occurred in those whose asthma began after the age of forty-five, but typical symptoms and pathological changes can also occur in younger persons.

Since this article was written, Unger, in his book on "Bronchial Asthma"<sup>105</sup>, just published, reports four more cases in which death was due to asthma; autopsies showed "typical" asthmatic lungs.

Hagen<sup>42</sup> studied the cervical ganglia removed from seven patients because of severe asthma. Sections revealed pathological changes in almost all ganglia, with disharmony of processes with hypertrophic glomerulus-like ball formation. Vacuolation and granular degeneration were frequent in the body ganglion and the processes,

and there was an increased number of multinuclear ganglion cells. These changes may perhaps explain some of the secondary symptoms of bronchial asthma. Brandes, Cooke and Osborne<sup>10</sup> report an unusual case. A thirty-one-year-old man had recurrent attacks of dyspnea, without fever, for three successive winters, and dyspnea persisted during the year preceding death from asphyxia. Allergy studies were negative. Autopsy revealed emphysema, aberrant growth of bronchial lymphoid follicles, sclerosis of the small branches of the pulmonary arteries and arterioles, and cor pulmonale.

Harkavy<sup>16</sup>, in a discussion of fifteen cases of asthma, including four that came to autopsy, concludes that:

1. Bronchial asthma is an expression of hyperergic vascular response, reversible or irreversible
2. The tissue changes do not represent disease entities but rather qualitative and quantitative degrees of hyperergic and anergic response, and
3. The syndromes dependent on such vascular reaction in the myocardium, pericardium or other serous membrane, and expressed as cardiac insufficiency, constrictive pericarditis, or polyserositis, may therefore be attributed to an allergic mechanism.

## SYMPTOMATOLOGY OF ASTHMA

Thomas and Taylor<sup>100</sup> define "allergic bronchitis" as "an allergic reaction to one or more specific sensitizing substances in a susceptible individual, and is characterized by a chronic, recurring, or paroxysmal cough. In most instances, it is not associated with dyspnea, and it usually occurs in the absence of any upper respiratory tract infection or intrathoracic pathologic condition which otherwise might account for the bronchitis." Allergic bronchitis occurred in 12 per cent of all patients admitted to the allergy department of the Cleveland Clinic. Almost all cases also had an allergic rhinitis; onset in 46 per cent followed some acute respiratory infection; hereditary influences were similar to those found in bronchial asthma; physical and x-ray examinations were not conclusive; skin tests were frequently positive. The treatment was that used for asthma and gave excellent results, with only 15 per cent failures. Unfortunately, no sputum tests for eosinophilia were included. This condition is important because adequate and early diagnosis and treatment will usually prevent the onset of asthma.

Classifications of asthma have been proposed by Cohen<sup>18</sup> and Coke.<sup>19</sup> Cohen stresses the elaboration of histamine or an H-substance by the cells when excited by extrinsic factors; symptoms are then due to the action of this substance on the cells of the bronchial tree. He classifies cases into extrinsic, intrinsic, and combined. Coke, from England, again classifies asthma into: (1) allergic; (2) microbic, and (3) aspirin-sensitive or mixed groups. These groups may overlap. Autogenous bacteriophages have given good results in the infectious cases. Coke complains that the allergic cases are being neglected by British physicians, and warns that, if the neglect continues, the municipal authorities will probably run the asthma clinics with the assistance of physicians cognizant of the proper care of asthma.

Swineford and Weaver<sup>97</sup> show that there has been too much emphasis on skin-testing and not enough on history-taking. They present a nice outline for taking histories, and criticize many books on allergy because they do not detail important questions to be asked patients. Skin tests are nicely evaluated by Steele<sup>93</sup>, who points out once again the proper technique, and stresses the fact that skin tests are only a valuable adjunct to the history and clinical findings and should not be given undue importance. He correctly warns against the use of combined extracts for testing. Stoesser<sup>96</sup>, working with children, uses the puncture method on the back; positive tests for foods are of the greatest value in infants, inhalants in the pre-school age, and pollens up to and through puberty. Inhalants are much more important than foods, even in children.

Randolph<sup>85</sup> describes a new method of counting white cells. His diluting fluid contains phloxine and methylene blue in equal parts of propylene glycol and water. The eosinophiles and other white cells are counted directly in the blood chamber, and the eosinophiles are easily seen. It is therefore not necessary to make the usual stained differential smears.

Papers on varied subjects have also appeared. Herrioz Ballesteros<sup>7</sup> discusses impaired nutrition as an allergic manifestation. It is especially frequent in asthmatic children, one-third of whom are underweight (15 to 50 per cent); thoracic deformities are common. Proper anti-allergic treatment markedly improves nutrition. Thomas and House<sup>99</sup> report a case of status asthmaticus complicated by drug allergy, sinus infection, and dermatitis medicamentosa due to neoarsphenamine. Edema of the legs also occurred when sulfadiazene was given for fever associated with the asthma. Rackemann<sup>82</sup> discusses new theories concerning patients whose asthma starts late in life and progresses despite all treatment. These are "intrinsic" in that no evident allergen has been discovered, yet the blood eosinophilia is high, 13 to 20 per cent in one case. He believes that sinus surgery rarely cures, and he suggests operation only when the condition of the sinuses is so bad that intervention is indicated without regard to the asthma. He is intrigued by the relationship of asthma to the adrenal gland, especially the cortex, but, unfortunately, has nothing new to offer in the line of treatment.

Tocker and Davidson<sup>101</sup> reviewed 386 patients at the Sea View Hospital for Tuberculosis; 3.1 per cent of the patients also had bronchial asthma; (this percentage seems high). They point out that skin reactions to allergens are weaker and more delayed than in non-tuberculous allergic individuals. They were very careful in differentiating true bronchial asthma in these tuberculous patients from the "asthmatic" breathing caused by tuberculous bronchopulmonary pathology. Interesting: asthmatic symptoms tend to improve with activity of the tuberculosis and to recur with healing—another probable instance of nonspecific action. Asthmatic attacks should be combatted because they aggravate the tuberculous infection, and artificial pneumothorax is apt to cause exceptional dyspnea in patients with asthma and tuberculosis.

Pulmonary complications, especially atelectasis and spontaneous pneumothorax, are not rare in asthma; subcutaneous emphysema is less common. Atelectasis probably occurs more frequently than we can prove, and Cole, Nalls, and Buis<sup>20</sup> report four more cases of asthmatic atelectasis which simulated pneumonia. Diagnosis was aided by the x-ray and by bronchoscopy and bronchogram. Sulfonamides were not helpful, but when the obstruction of the bronchus, cause of the atelectasis, was removed by coughing up or bronchoscopically removing the plugs, the symptoms rapidly abated. Fever, pain in the side, dyspnea, and nonproductive cough are the chief complaints.

Trowbridge<sup>103</sup> discusses spontaneous pneumothorax in asthma and advises against removal of air. Engelhardt and Derbes<sup>30</sup> review twenty cases in the literature, in only two of which autopsy was done; their own patient had asthma, developed spontaneous pneumothorax, and died suddenly. Autopsy confirmed the diagnosis. They urge against thoracocentesis although they repeatedly tapped their patient. They believe that the air escapes into the pleural cavity by rupture of a valve vesicle. Field's patient<sup>33</sup> was a girl of four who eventually recovered despite the fact that she had bronchial asthma, subcutaneous emphysema with massive collapse of the left lung, and spontaneous pneumothorax of the right chest. Fortunately for the patient, else she could hardly have survived, there was an interval of 15 days between the asthma and the initial subcutaneous emphysema with collapse of the left lower lobe, and the second episode characterized by asthma, collapse of the left upper lobe and spontaneous pneumothorax on the right side. This combination is very rare. Francis<sup>36</sup> adds two cases in which subcutaneous emphysema occurred



during acute asthma. These cases are dramatic but not serious. The rupture occurred during a severe paroxysm, with resultant dyspnea, cyanosis, and swelling of the neck and adjacent parts. Crepitation was prominent, and the air was absorbed in seven and ten days, respectively.

Day<sup>23</sup> says that "diaphragmatic dyspnea" is the most common disorder of the respiratory system in the British army. The cause is faulty diaphragmatic function, and appears late in military training, with physical signs suggestive of emphysema. Fluoroscopic examination reveals slight, absent, or paradoxical excursion. Breathing exercises are indicated. There are two recent articles on paroxysmal cardiac dyspnea (cardiac asthma). Karmally<sup>58</sup> gives a nice differential diagnosis from bronchial asthma. For attacks of cardiac asthma, he advises morphine, venesection and rest; constriction of the veins in both arms and legs may help, and oxygen may also be necessary. Harrison<sup>48</sup> agrees with this therapy.

#### TREATMENT OF ASTHMA

Many articles on various phases of treatment have recently been published. Most offer refinements, and many are surveys of methods already in use.

Prevention of asthma is very important, and we are on the threshold of a campaign to prevent or at least to lessen the incidence of asthma in children. Much can also be done to prevent asthma in adults. Gray and Albert<sup>41</sup> discuss eight individuals with pre-asthmatic symptoms, e.g., nasal congestion, sneezing, rhinorrhea, cough, or dyspnea. Asthma developed only when exposed to occupational dusts, e.g., feathers, furs and fur dyes, flour, cadmium fumes (platers), and insecticides. Removal brought relief. Allergic patients should be excluded from occupations with such dusts. Derbes and Winsor<sup>26</sup> add laboratory workers, food handlers, jewelers, beauticians, pharmacists, and chemists to the list of occupational allergic hazards. Although change of occupation is the best therapy, many workers will not or cannot do this; it is therefore necessary to take all possible measures for removing or lessening the amount of such dusts; hyposensitization with environmental dust extracts may be very beneficial. Many of their patients were over forty and might have been wrongly classified as "intrinsic," with resultant neglect. The control of nonoccupational allergens is also important.

Inhalation therapy has again been stressed. Barach<sup>6</sup> has outlined a long and involved series of procedures for status asthmaticus.

He advises:

- (a) Inhalation of helium-oxygen mixtures or oxygen alone
- (b) Aminophyllin intravenously, orally, and by rectal suppositories
- (c) Potassium iodide
- (d) Neosynephrin inhalations by nebulizer
- (e) Sedation, preferably by sodium luminal

When attacks are severe, he uses:

- (f) Ether, per rectum
- or
- (g) Intravenous injections of typhoid vaccine

He also advises demerol or dilaudid. (Demerol is often efficient and rarely harmful, but dilaudid is an opiate and as dangerous as morphine, and should not be used in any attack of asthma). Barach continues these procedures even after improvement has set in—"repeated bronchial relaxation."

Weisser<sup>110</sup> has a nice paper on chronic asthma. Treatment consisted of massage, rhythmic compression of the chest, resounding breathing exercises, and regulated gymnastics, e.g., boxing, jujitsu, and calisthenics. These procedures were given daily for many months, even years. Tolerance for exercise was gradually increased, and dyspnea due to exertion was decreased because the patient's vital capacity increased as his expiratory time diminished. Results: thirteen of twenty-nine children free from attacks for three and one-half years, ten improved, six no

relief. Of ten adults, one free from attacks, five improved, four not improved. The procedures are therefore especially valuable in chronic asthma in children. Gay<sup>38</sup> also advocates chest massage in such cases; his patients blow air from one two-gallon bottle to another and then back again. This therapy seems very logical and should be more widely adopted.

Vaccine therapy is described by Prince<sup>78</sup>, Boyd<sup>9</sup>, and Brunk.<sup>15</sup> Prince, in discussing asthma complicated by respiratory infection, stresses the importance of examining sputa for bacteria and for the type of cells. Chemotherapy is excellent in many cases, especially if pneumococci are present. He uses autogenous and stock vaccines, depending on the number of specific bacteria. If stock vaccines give good results they are continued. If not, autogenous vaccines are used. He rightly frowns on radical sinus surgery unless frankly purulent sinusitis is present. Boyd advocates injections of B. H. (Hoffman's bacillus) vaccine in various allergic disorders in which accepted methods of treatment have failed. He begins with 0.10 c.c. and increases cautiously, with due regard for local or systemic reactions, up to 1.0 c.c., and keeps up this dosage for months or years. Brunk, in a study of 500 private patients, determines the antigen-producing properties of organisms recovered from foci of infection. He uses about 35 antigens, including the colon bacillus, micrococcus catarrhalis and the ordinary strains of staphylococci and streptococci. The tests also show the specific organism to which the patient is sensitive. Then cultures of all available excretions, including the urine and stools, are tested for the responsible antigen. Once the offending organism and focus of infection are determined, the treatment is primarily surgical, i.e., removal of the focus. Vaccines made from the specific organisms are very potent, and must be given in small doses. Deficient complement in the patient's blood stream indicates a bad prognosis and constitutes a definite contraindication to surgical interference. The methods of Boyd and Brunk should be repeated by other investigators.

Drug therapy continues to draw attention. Brown<sup>12</sup> gives a list of more than 200 advertised commercial products, most of which are not Council Accepted. Some are ethical, others not. The composition of each is noted, and is very useful. Brown suggests the use of the best possible medication at the lowest possible price. Another list of patent medicines used in asthma is also in Unger's new book on Bronchial Asthma.<sup>105</sup>

Brown, Wilder and Schwartz<sup>14</sup> studied local reactions in rats and rabbits from intramuscular injections of corn, cottonseed, sesame and peanut oils. Corn oil was the least viscid, and remained fluid to minus 15° C. Chemical agents used as preservatives are irritating. Corn and sesame oils produced the least amount of local reaction in the muscles of these animals, peanut oil the most marked. Harris and David<sup>47</sup> gave 50 mg. ephedrin sulfate daily to seven normal individuals for three to four weeks. Within three weeks, there was an average rise of one-half million red blood corpuscles and a corresponding increase in hemoglobin. The white cells were not changed. After four weeks of therapy, the red cells and hemoglobin usually returned to normal even though the use of ephedrin was continued. Therefore, the prolonged use of ephedrin is not harmful to the blood.

Demerol, the new analgesic and substitute for morphine, is discussed by Yonkman, Noth and Hecht, and by Noth, Hecht and Yonkman.<sup>11</sup> Pharmacologically, demerol resembles atropine in its anticholinergic action with production of mydriasis, suppression of saliva, and antivagal action on the heart, bronchi and intestines. It resembles papaverine in its spasmolytic action, directly relaxing the musculature of the bronchi, intestines, uterus, and blood vessels. It resembles morphine in its analgesic, sedative, and euphoric effects. It is a relatively safe drug. Clinically, it is given orally or intramuscularly in doses of 75 to 100 mg. and may be repeated one to eight times daily. For children, dosages of 10 to 75 mg. are recommended. If given intravenously, demerol should be diluted and injected slowly. The results are often

good. In one patient, however, oral administration was followed on two occasions by severe vasomotor collapse, bronchospasm, nausea and vomiting. Addiction is not as pronounced as with opiates.

Hansel<sup>44</sup> gave  $\frac{3}{4}$  grain nethamine hydrochloride and 2 grains of theophylline isobutanolamine to 250 patients over a period of three years. The symptoms associated with allergic rhinitis and asthma were satisfactorily lessened. Nethamine has ephedrine effects without the unpleasant side effects. The other drug is a xanthine compound, similar to aminophyllin but more soluble and less toxic. The combination was made up in scored tablets, and the average optimum adult dose was  $\frac{1}{2}$  tablet; in children  $\frac{1}{4}$  tablet. The combination can also be used intravenously, intramuscularly, or in rectal suppositories.

Merrill<sup>67</sup> reported three deaths in "asthmatic" patients during or shortly after intravenous injections of 0.25 gm. of aminophyllin. One might conclude that the drug is dangerous in bronchial asthma. Unger<sup>106</sup> analyzed these cases, and showed that all three were suffering from severe cardiovascular disorders, and suggested that the drug may be dangerous when given intravenously in cardiac diseases. In uncomplicated bronchial asthma, however, the slow intravenous injection of aminophyllin is highly beneficial and not at all dangerous. An occasional episode of nausea may result.

A very interesting paper comes from India. Chatterjee<sup>16</sup> gave adrenalin and atropine but was unable to control asthma in a twenty-eight-year-old woman who had had asthma since the age of five.

"She was tired and exhausted, groaning and moaning at each breath, appealing to humanity for help, seeking the mercy of God, begging the doctor for relief or even welcoming death. I gave her the same injections as before but moved too much by patient's misery, I was determined to give her some relief and rest. I gave morphine gr.  $\frac{1}{6}$  with a clean conscience. The result was marvelous. Within two minutes the patient felt relieved, thanked me for saving her life and gave me my dues and all previous dues up to date overwhelmed with gratitude. She took a little barley and asked her mother to clean the bed at once for she wanted to sleep. I left the place at 9:30 p.m. I was called again at 10 p.m. I found her pulseless with respiration very slow, 7 per minute. I declared the case as hopeless. The patient died at about 11 p.m."

The doctor concludes: Don't give morphine in asthma. This dramatic description needs no comment.

Reactions continue to occur. Applebaum<sup>4</sup> describes cerebrovascular accidents in two young males who had been given their first injections of 0.50 c.c. of 1:1,000 epinephrin for asthma. The first man became restless and apprehensive in a few minutes; speech difficulty and right hemiplegia and right facial paralysis followed. There was moderate vasoconstriction of the retinal vessels. The findings began to subside in a few hours, and in five weeks, the soldier was normal, except for a slight facial palsy. The other patient quickly developed headache, nervousness, palpitation, mental symptoms, and paralysis of the left arm and leg and the left side of the face. This episode was completely gone in two hours. A few similar cases have been previously reported. Deissler's patient<sup>25</sup> had asthma and hay fever and also a well-compensated rheumatic double mitral heart condition. Through an error in dosages and after an interval of thirty-four days from her previous injection, she received an increase of 20 per cent of pollen extract. She remained in the office 20 minutes, and revealed the usual local reaction. On the way home she coughed up thin watery pinkish fluid and became dyspneic and cyanotic. Her blood pressure dropped to 80/50, with pulse 140 and many fine moist râles through both lungs. The usual treatment for allergic reactions (cuff, epinephrin and intravenous aminophyllin) gave no relief, but morphine caused quick relaxation. This was not the usual allergic reaction, but was an instance of acute pulmonary edema following

an overdose of antigen. Unfortunately, the patient's cardiac reserve has not completely returned to normal, and she now takes 0.1 gm. digitals daily. Bigler<sup>8</sup> has an interesting paper on allergic reactions resulting from injections of toxoids; fortunately, no deaths have as yet been reported. The peptone in the mixture seems to be the responsible agent.

Ethylene disulfonate is still a disputed remedy. Wasson<sup>108</sup> used it with good results in children with asthma; control cases were also studied. Bartlett<sup>7</sup> tried it in 247 consecutive allergic conditions in children, with satisfactory results in 86.64 per cent. The average number of 2.0 c.c. injections per patient was 1.41. Dr. Chauncey Leake, Professor of Pharmacology and Dean of Texas Medical School<sup>100</sup> reports that, from a scientific point of view, the claims of the manufacturer could not be duplicated. He believes the drug "will eventually rest in the limbo of forgotten therapeutic agents."

Tainter and his associates<sup>98</sup> state that ethylnorsuprarenin is useful in the treatment of asthma and possibly preferable to epinephrin for those patients in whom the latter drug gives undesirable side effects. The drug acts like epinephrin as a sympathomimetic, but does not raise blood pressure, and in animals it is 1/120 as toxic as epinephrin. Confirmation by other workers is urged as such a drug is desirable.

Prickman and Gelbach<sup>76</sup> report that postoperative pulmonary complications occurred in only 15 per cent of 142 asthmatic patients who experienced major surgical procedures. Pneumonia occurred in six cases, atelectasis in six, and severe asthma in four. The incidence was twice as high after operations in the upper abdomen as in the lower. Two deaths occurred, a mortality rate of 1.4 per cent. Patients with infectious asthma were more apt to develop pneumonia, and spinal or intravenous anesthesia was preferred. In fifty-eight patients who received ether, ten developed pulmonary complications. The usual allergy management was given, and the authors suggest postponement until warm weather, if possible, of operations in patients who have infectious types of asthma.

Nonspecific treatment is further illustrated by three other articles. Fiessinger and his associates<sup>34</sup> had a patient with severe asthma; there were 9,100 white cells in the blood, with an eosinophilia of 13.5 per cent. Typhoid fever developed, the white cell count dropped to 4,700, and the eosinophiles disappeared as did the asthma. Kaplan and Rubenfeld<sup>57</sup> discuss roentgen treatment in sixty-six asthmatic patients, most of whom were thirty to fifty years of age; 72.7 per cent were relieved. They also note that:

- (a) the longer and more severe the illness, the more favorable the response
- (b) aggravation of symptoms often preceded amelioration
- (c) recurrence of attacks are unfortunately the rule rather than the exception

Despite this latter observation, roentgen therapy is definitely worth while in cases of continued asthma. Miley, Seidel and Christensen<sup>68</sup>, in eighty cases of intractable asthma, applied the Knott technique of ultraviolet blood irradiation. The patient's blood is withdrawn from a vein, citrated, and passed through a Knott hemoirradiator, a precision machine which automatically exposes the blood to strong ultraviolet energy and returns it to the venous circulation of the patient. Treatments are given every four to six weeks and then at longer intervals and finally three to four times a year. The authors state that the Knott technique was a safe and efficient method of controlling intractable bronchial asthma in forty-five of fifty-six patients who received constant treatment and observation.

The usual number of "general" papers appeared. Bray<sup>11</sup>, discussing status asthmaticus, advises adrenalin in suspension (not oil), ether and oil rectal enemas, aminophyllin, nicotinic acid, bronchoscopic aspirations, inhalations of CO<sub>2</sub> and steam (not oxygen), breathing exercises, and short wave therapy to the chest. Sulfonamides

have not been successful in his hands. Prickman and Gelbach<sup>77</sup> discuss the symptomatic treatment of seasonal hay fever and asthma. Moskow<sup>70</sup>, from South Africa, occasionally gives morphine or inhalations of chloroform in acute asthma (both are dangerous). Other papers of a general nature have been written by Davison<sup>22</sup>, Rackemann<sup>83</sup>, Skinner<sup>82</sup>, and Schonwald.<sup>80</sup> Salazar Mallen<sup>65</sup> says that allergic diseases are common in Mexico City. He has examined about 3,000 patients, most of whom had "major" allergic conditions. One thousand of these were from the charity clinic at the General Hospital. Asthma and vasomotor rhinitis constituted 62 per cent of 1,687 private cases. Rackemann<sup>84</sup> has his usual excellent review of 1943 reports on allergic diseases, including asthma. Jiménez Díaz, from Madrid, gave four lectures on allergy at The Faculty of Medicine at Buenos Aires.<sup>55</sup> Among other items, he recognizes that desensitization is of little value in infectious types of asthma.

Olson, Appel and Necheles<sup>71</sup> studied a dog who had severe attacks of asthma, but autopsy revealed cardiac disease, not bronchial asthma. Red-green blindness was present in 12 per cent of Molholm's young male allergic patients<sup>69</sup>, an incidence three times higher than in normal males of that age. He believes that this possibly indicates that some cases of asthma in boys may depend in part on a sex-linked recessive factor.

The treatment of bronchiectasis is rightly swinging more and more toward lobectomy, especially in patients with a good surgical prognosis and in localities where good chest surgeons are available. All other measures, including postural drainage, bronchoscopic aspirations, chemotherapy, radiation, vaccines, and even inhalations of penicillin, have proved disappointing. The role of nasal sinusitis as a factor in producing bronchiectasis is still disputed. Recent articles on this subject have been written by Alexander<sup>1</sup>, Goodale<sup>40</sup>, Hart<sup>49</sup>, and Hinshaw and Schmidt.<sup>52</sup>

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# REVIEW OF THE LITERATURE ON HAY FEVER FOR 1944

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In spite of the demands upon the time and energy of the profession, a goodly number of articles on hay fever have appeared in the literature this year and detailed information on this phase of allergy is to be found in several recently published books.

Gradually the importance of allergic diseases in military medicine is being recognized. Although the mobilization regulations with respect to hay fever remain the same, French and Halpin<sup>14</sup> report a definite increase in the number of cases seen. This is due mainly to the difficulty facing medical officers of the induction boards, especially in examining candidates in a non-pollen season. As stated, a "great degree of decision, diplomacy, and judgment is required to determine the fitness of a candidate and the compatibility which may or may not exist between military service and his potential degree of allergic disability."

Conferences and short courses of instruction have been given in station and general hospitals of the Fourth Service Command to stress the importance of allergy. By prompt diagnosis and treatment many allergic soldiers have been able to remain on full duty status with a minimum of time lost from training. A close degree of liaison between allergists and induction boards has brought about a more rational plan of rejection or acceptance. Since conditions of environment and diet are difficult to control in the Army, the results of therapy have not equalled those in civilian life.

Statistics from the allergy section of a station hospital in Florida given by Gold and Bozmore<sup>18</sup> also stress the military significance of allergy. These authors describe a method of preinduction consultation service for the local armed forces induction station which has proved an excellent means of eliminating allergic inductees. If hay fever symptoms are not accompanied by asthma, full duty, with preseasonal or co-seasonal desensitization therapy, is advised. If asthma is associated and is mild, the soldier is reclassified and appropriate desensitization is given.

In another article by French and Halpin<sup>15</sup> there is a summary of the findings of the allergy clinics of the Fourth Service Command for the past two years. Of a total of 32,046 allergic patients, seen in 67 clinics, 5,372 had symptoms of seasonal hay fever of sufficient severity to lead them to seek relief. Uncomplicated seasonal hay fever did not warrant a certificate of disability discharge—in only 106 cases was discharge necessary. Very good results were obtained by the use of pre-seasonal and co-seasonal therapy with the administration of pollen extract in conservative low dosages.

In the field of aviation medicine Hampton and Rand<sup>21</sup> stress the importance of a good plan of diagnostic approach. In the allergy section and clinic of a regional hospital of an aviation cadet center in Texas, from August, 1942, to August, 1943, there were 921 cases of respiratory allergy in a total of 1,238 allergic diseases. Thus, hay fever, vasomotor rhinitis and asthma accounted for three-fourths of all allergic diagnoses, with pollinosis accounting for approximately one-third of this group. According to Army regulations, issued in 1940, hay fever or any history of hay fever was disqualifying for aviation training but subsequently this was changed so that only individuals who had had hay fever two years prior to examination, regardless of past hay fever history, were disqualified. The following plan has been used to arrive at an interpretation of the degree of hay fever and the prognosis in relation to flying: as accurate a history as possible, tests with common inhalants and pollens; titration of skin sensitivity to pollen extracts; a study of nasal cytology



and physical examination. Association with asthma is considered indicative of a severe hay fever; with eye symptoms moderate or severe; and nasal symptoms alone, as mild or moderate. A total of 283 candidates were disqualified because of allergic disorders and 135 of these because of hay fever.

Rudolph<sup>30</sup> emphasizes the importance of recognizing atypical cases of hay fever especially where significant signs and symptoms are not present in number and sequence and where seasonal limits are not definite. These conditions are often difficult to identify and are responsible for the loss of many days of active duty.

A comparative botanical survey by Lamson, et al.<sup>25</sup>, brings out the problems that arise in California, "where unlike the East, there is no extensive area in which the botany is characterized by a few identical types, it is practically impossible to find an adequate description of the botany of towns and cities, and there is a striking ignorance of the variations in flora." A comparative study is made of Barstow, California, a town at an elevation of 2,106 feet with vegetation of the desert-plain type, and Santa Ana, Calif., a coastal city at an elevation of 135 feet. Tree pollens, except for poplar and willow, are not of general significance; in the desert, grasses either do not grow or their season is so brief that they contribute little; while the coastal area has an extensive and perennial grass problem. Compositae are not the most important weeds of the desert but "salt loving" weeds are outstanding offenders. Certain prototypes are emphasized for each community and there is some overlapping, although dissimilarity is the rule.

Graphs of pollen concentrations for the Phoenix area and illustrations of common pollens are presented by Randolph<sup>36</sup> and McNeil. Their findings for the most part confirm the conclusions previously drawn by others.

Pollen surveys made by MacInnis<sup>82</sup> in South Carolina reveal that there is no month of the year when pollen is absent, there are exceptionally high pine and nut counts, especially in "good nut years," grass pollen is found during the entire year, and the ragweed season lasts longer than the usual six weeks.

From "studies on plants, pollens and patients," Brown<sup>4</sup> has found that nearly all of the seasonal hay fever in the District of Columbia is due to relatively few pollens. There is an early spring season due to tree pollens; late spring and summer due to grass and plantain; and a fall season due mainly to ragweed.

Penfound<sup>35</sup> has reported the results of six years of observation in the pollination of anemophilous trees in New Orleans. Because of the semitropical coastal climate the conditions for plant development are excellent throughout the entire year. Some species even bloom throughout the year. The initial anthesis begins five weeks earlier than at Memphis and nine weeks earlier than at Chicago. The total anthesis periods of the trees in New Orleans are almost double those of the same species in Memphis and Chicago. A given species of trees in New Orleans averages 35 days earlier than at Memphis and 63 days earlier than at Chicago. The blossoming of trees is initiated at Memphis and Chicago before the average monthly temperature reaches 45°F. whereas the lowest average mean temperature is not lower than 54.3°F. in New Orleans.

Mexico and other regions to the south of us have come in for their share of surveys. Salazar Mallen<sup>29</sup> disagrees with those who have stated that latitudes and altitudes of Mexico make pollinosis unimportant and that ragweed does not flourish in the valley of Mexico. Pollens do exist and ragweed sheds its pollen everywhere from July to September but this pollination occurs when the rainy season is heavy so that there never is more than 25 grains per square centimeter a day recorded (based on sedimentation counts). The list of pollens causing allergic respiratory symptoms includes, besides ragweed, Bermuda grass, Johnson grass, green ash, pigweed, Russian thistle, cedar tree and a few others.

In Rio de Janeiro there is only one pollen season, according to Greco and Oliveira Lima<sup>20</sup> and that is the grass season which extends from the middle of

May to the middle of June. A minute amount of amaranth-chenopod pollen is found infrequently and has no definite seasonal character.

In a study of pollen counts in 11 Brazilian cities Greco<sup>19</sup> found grass pollen in sufficient amounts to cause hay fever, the most important grass being *Molinis minutifolia* (capim gordura). So far no cases of hay fever have been found among the pure natives.

Oliveira Lima and Greco<sup>26</sup> claim that there are several reasons for the rarity of pollinosis in Brazil, one being the scant interest of physicians in this subject and the other errors in diagnosis. A third factor is the low-grade sensitivity of Brazilians to the pollen of *Lithrea Moleoides*.

Molds are considered by Passarelli<sup>33</sup> to be important allergens in Rio. These commonly found are *penicillium*, *hormodendrum* and *aspergillus*. *Alternaria* is rarely seen.

Pollen and pollinosis in Argentina have been the subject of a series of articles by Herraiz-Ballester and Monticelli.<sup>1</sup> They report that the coastal variety of *Beta vulgaris* grows abundantly near Bahia Blanca in Buenos Aires. This plant, the most frequent cause of pollinosis, produces large amounts of pollen between October and the second week of December. Pollination of this chenopodiacea herb precedes or accompanies pollination of graminaceous plants. This fact is of importance in connection with therapy.

Esandi et al.<sup>11</sup>, also in Argentina, studying familial and hereditary factors in pollinosis conclude that, although symptoms may appear earlier in patients with a family history of allergy, in Bahai Blanca at least, the hereditary factor is not essential. Pollen seems to be capable of sensitizing subjects even if there is no predisposition.

*Ambrosia tenuifolia* which pollinates from November to April is the most important pollen offender in Argentina, according to Ruiz Moreno and Spegazzini.<sup>31</sup> In Buenos Aires this pollen is found only during the months of January, February and March.

Dumm and Zarate<sup>9</sup> find that *artemisia verlotorum* Lamott causes pollinosis in the city of La Plata.

Vaughan<sup>45</sup> compares the relative importance of the different plants causing hay fever in the two Americas, giving in tabular form the dates of pollination of about three dozen varieties important in the United States with comparative dates for Argentina. As great a variety of pollens are found in the different parts of South America as in the various sections of the United States, while the flora of Mexico is quite different from that of the northern part of the continent. Pollinosis should be less common in tropical than in temperate zones as more plants are pollinated by insects. Inquiries in Mexico, Central America and South America would seem to confirm this opinion.

Chobot and Dundy<sup>5</sup> studied a group of patients in the New York area who complained of hay fever and asthma from the last week of July until August 10 and whose symptoms could not be ascribed to inhalants, such as dust, feathers, or to molds; or to upper respiratory infections. The suspected pollens included Marsh elder (*Iva frutescens*), cultivated corn, wild rice and cocklebur. The problem of determining the importance of these pollens was attacked by a procedure combining positive skin tests, clinical observation for at least one season, and treatment during the following season, with a critical evaluation of the results obtained. The authors conclude that these pollens may no longer be disregarded in the New York area; they are present in the atmosphere in sufficient concentration to affect some patients and that treatment relieves symptoms.

Rogers<sup>38</sup> reports that in eastern Pennsylvania pollens other than grass and ragweed are rarely the sole cause of hay fever but they frequently complicate or act as minor synergens to the major pollens. Treatment for these minor pollens

(English plantain in particular) is more satisfactory than it is for the major pollens.

From an Australian military hospital comes a report by Hand<sup>22</sup> of two cases of dermatitis from capeweed, one associated with symptoms of hay fever and the other with skin manifestations only. The first patient gave marked positive patch reactions and had a marked exacerbation of his dermatitis following a patch test with the flowers of capeweed but gave vegetative patch reactions to the stalk and leaf; and there were marked positive transfer reactions to capeweed flower and pollen but negative reactions to the essential oils of the capeweed plant. The patient with dermatitis only gave positive patch reactions to the capeweed flower, stalk and leaf; essential oil and pollens but passive transfer tests were negative.

Francis<sup>13</sup> believes that localized atrophy of subcutaneous fat may result not only from injections of insulin but from any type of injection regardless of the material injected. Such atrophy was observed following repeated injections of grass pollen extract in a woman who, although a diabetic, had taken no insulin for over a year.

Deissler<sup>8</sup> reports the sudden precipitation of pulmonary edema in a patient with long-standing mitral disease as a result of an overdose of pollen antigen. Respiratory distress with the expectoration of a thin pink watery fluid began twenty minutes after the injection and did not respond to the usual treatment for systemic reactions (epinephrine and aminophyllin). Prompt relief followed the injection of morphine. The patient's cardiac reserve was lowered for some time following the reaction and digitalization was necessary.

Because the incidence of asthma and hay fever is about twice as great in boys as in girls, Molholm<sup>30</sup> suggested that one of the hereditary factors upon which some cases of asthma and hay fever depend might be in part transmitted as a sex-linked recessive factor. He found in a group of 165 asthmatic male patients and 192 male hay fever patients an incidence of red-green color blindness of 8.4 per cent which is about twice as great as the incidence of about 4 per cent among unselected males.

Tocker and Davidson<sup>43</sup> find the incidence of asthma and hay fever in patients with active pulmonary tuberculosis approximately the same as in the normal population.

Reports on the use of vitamins in hay fever continue to appear. Newbold<sup>32</sup> found no evidence that ascorbic acid had any significant effect upon the allergic skin reactions due to the intracutaneous injections of short ragweed extract.

Hebald<sup>23</sup> gave a group of ten untreated hay fever patients 500 mgs. of ascorbic acid daily and weekly injections of an alkaline saline diluting fluid. The results were uniformly poor, leading to the impression that vitamin C is not an effective form of treatment for hay fever.

However, Pelner<sup>34</sup> reports that he was able to increase the tolerance of an extremely sensitive ragweed patient by the simultaneous injection of  $\frac{1}{2}$  c.c. of sodium ascorbate so that the patient was ultimately able to tolerate a dosage of 1,500 units of ragweed extract without systemic reactions.

Since edema is one of the manifestations of allergy and it also occurs in experimental animals deprived of vitamin E, Glaser and Dam<sup>17</sup> thought pollinosis might be a suitable allergic disease in which to test the use of vitamin E. Synthetic vitamin E by mouth in doses of 250 mg. per day was of no value in the treatment of a small series of cases of ragweed pollinosis.

Results of oral pollen therapy have been disappointing although occasionally a patient is found who apparently is benefited. The thought that the poor results might be due to inactivation of pollen by the digestive juices prompted Hecht, et al.<sup>24</sup>, to study the absorption of pollen from the gastro-intestinal tract. By means of passive transfer studies it was found that normal or artificially elevated

gastric acidity decreases the absorption of orally administered pollen antigen while a reduction of acidity increases the absorption.

Because the antigenic power of grass and ragweed pollen has been shown to be diminished or abolished by gastric digestion it was thought that oral pollen therapy might be more effective if administered in enteric-coated capsules. By means of passive transfer studies, Thiberge<sup>42</sup> was able to demonstrate, in four out of fourteen nonallergic patients, the absorption of an unaltered pollen when enteric-coated capsules of grass and ragweed pollen were given.

Sherman and Barrow<sup>40</sup> studied a group of forty patients who experienced repeated constitutional reactions from injections of pollen extract to determine whether these patients exhibited an abnormal degree of reactivity in either the cutaneous or the mucosal shock tissue. The conjunctiva was used for studying mucosal reactivity and comparative titrations of the cutaneous and conjunctival reaction were made. In an experimental group of forty it was found that 50 per cent showed a reduced ratio of skin and conjunctival sensitivity. In a control group of treated patients with no constitutional reactions only 17 per cent showed a reduced ratio. The authors believe that the reduced ratio was probably the result of an excessive hypersensitivity of the mucous membranes, since there was no evidence of a diminished cutaneous reactivity.

Rockwell<sup>37</sup> describes a method for the standardization of pollen extracts as molar solutions and gives a formula for the conversion of molar concentration to molar units. Using the phosphotungstic acid precipitate only two determinations are necessary: total nitrogen and the total free  $\alpha$ -amino nitrogen. Not only is this method considered a more accurate one for standardizing extracts, but by studying the free  $\alpha$ -amino nitrogen it is possible to follow the aging of extracts.

Durham<sup>10</sup> compared volumetric and gravity slide methods of obtaining samples of the ragweed pollen and alternaria spore content of the air. Two totally different volumetric devices recovered practically the same amounts, whereas simultaneously exposed gravity slides caught amounts varying greatly day by day. The greatest excess catch of ragweed on gravity slides usually occurred on days of highest wind velocity but the degree of inaccuracy could not be predicted. The rates of fall for various pollen grains cannot be calculated from the rate of deposit on outdoor gravity slides because of the unavoidable impinging effect of frequent wind currents. Practical considerations will necessitate the continued use of the gravity slide method but its inaccuracy should be recognized.

Berresford and Cooke<sup>2</sup> have described a pollen dehydrator, portable and easy to operate which will dehydrate pollen to virtual completeness in a few hours. It is believed that better keeping qualities will be found in pollens rapidly and completely dehydrated.

Cooke<sup>7</sup>, in reviewing the serological studies of the hay fever type of allergies, reminds us that "we understand little of the basic facts and that there are many problems still to be solved." The positive skin test itself is not a criterion of clinical sensitiveness, and the results of treatment leave much to be desired. There are still too many problem cases; those that do not respond to injections and those in whom systemic reactions frequently recur.

Another complete review of the immunology of pollen hay fever, that of Swineford,<sup>41</sup> emphasizes the great need for a technique simple enough to permit routine office titrations of the antibody response to treatment with pollen and other extracts, and a consequent true evaluation of the role of thermostable antibody. The prompt and lasting relief afforded by the use of a heated post-treatment serum in two patients who had been unsuccessfully treated, and in another who had had no treatment give strong support to the therapeutic usefulness of the blocking antibody.

An immunologic basis for the management of hay fever patients is also stressed

by Cohen.<sup>6</sup> He states that there is some question as to whether the thermostable antibody can explain completely the relief in treated hay fever patients but as yet it is the only mechanism that has been demonstrated which can explain the results on immunologic principles. Recently Cohen "has been working with a ragweed extract which produces good immunity but does not react with reagin and therefore produces no skin tests or constitutional reactions." With this material hay fever could be treated with a primary immunizing series of three or four doses in the first year and one dose annually thereafter.

Additional confirmation of the presence of a thermostable antibody has been given by Brown and Holden.<sup>3</sup> Since this antibody apparently binds the antigen, a passively sensitized site in which it is present requires a definite measured additional amount of antigen for neutralization.

In a continuation of her studies on the relationship between clinical hay fever and the blocking antibody, Loveless<sup>27</sup> believes that the treatment of hay fever may be shortened in those patients who have previously had a year of therapy. Twenty-four out of twenty-six patients with ragweed hay fever acquired good to excellent resistance when they were given "short booster" courses suited to their immunologic needs. Threshold tests of the conjunctiva and skin prior to the booster course gave some indications as to which subjects would give generalized reactions during therapy and tests repeated at the end of the course served as crude indices of the adequacy of therapy in newly acquired cases. Once the patient had been carried through a season of satisfactory clinical behavior, the associated levels of tolerance found in his eye, skin or serum were adopted as the goal for his future therapy. This method is still in the experimental stage "but it appears that the booster principle can be applied to the preseasonal management of pollinosis with success. It usually leads to optimal immunologic and clinical results in minimum time and without undue risk to the patient."

Gelfand and Frank<sup>16</sup> confirms the presence of a specific blocking antibody in the titre of ragweed-sensitive patients but finds that clinical results apparently do not depend upon high blocking antibody titres because the percentage of good results was identical in the patients who had low titres and those who had high titres.

A wealth of information on hay fever is presented by Urbach and Gottlieb<sup>44</sup> in their new book. Unusual is their inclusion of graphs of hay fever producing plants and pollinating trees for each of nine zones of the United States. These authors differ from most others in that they consider oral pollen therapy effective.

In Feinberg's<sup>12</sup> book a chapter on pollens and pollen allergy contributed by Durham and the discussion of allergy to fungi are excellent and of practical value to all who deal with hay fever. Mold allergy is given particular attention in response to requests of colleagues.

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# \* *In Memoriam* \*

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## AARON BROWN

On January 24, 1945, Dr. Aaron Brown died very suddenly of a heart attack in New York City at the age of sixty-one years. Doctor Brown was not a member of the College but he was a very tolerant individual who loved people and was willing to be of assistance to any physician in any way within his power and this was considerable because of his wide circle of intimate friends in all fields of medicine all over the country. Although an individual who was in no way aggressive, he was an intelligent, far-sighted physician. During his presidency of the Society for the Study of Asthma and Allied Conditions he had appointed committees and attempted to set in motion the machinery for carrying out many progressive ideas for the advancement of allergy which eventually reached their fulfillment years later when the American College of Allergists was organized, and subsequently also in the American Academy of Allergy when this was formed by the merger of the two older national societies.

Dr. Aaron Brown was the chief allergist of the New York University Medical School clinic, assistant attending physician at Bellevue Hospital, assistant clinical professor of medicine at New York University, consulting physician at the Bronx Hospital, and director of the allergy service at the Midtown Hospital of New York City. His membership included the American Association of Immunologists, the American Association for the Study of Allergy, the Society for the Study of Asthma and Allied Conditions, the American Therapeutic Society, the New York Academy of Medicine, the American Association for the Advancement of Science and the American Academy of Allergy. He was an honorary member of Sigma Xi.

Scientifically, Doctor Brown is probably best known for his popularization of the perennial method for the treatment of pollinosis which was original with him although it had possibly been thought of by others who did not develop the procedure as thoroughly as Doctor Brown. Besides his numerous scientific investigations, he was intensely interested in the practical aspects of allergy, and originated among many others such simple and effective ideas as the use of different colored rubber stoppers to indicate different types of solutions, and the "Aaron Brown tournique" which consists simply of the application of a snug-fitting ordinary rubber band above the site of the injection of an allergen extract in order to slow down absorption and ward off generalized reactions in individuals susceptible to these.

In the passing of Aaron Brown most of us have lost a beloved friend and all of us have lost an enthusiastic and helpful co-worker. The American College of Allergists is pleased to honor him with this memorial.

JEROME GLASER

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## ALFRED M. GOLTMAN

Dr. Alfred M. Goltman of Memphis, Tennessee, a charter member of the American College of Allergists, died November 11, 1944, at the age of 49. He was born at Nanticoke, Pennsylvania. He received his M.D. degree from Columbia University College of Physicians and Surgeons in 1921. Doctor Goltman received his training in allergy at the Balyeat Hay Fever and Asthma Clinic, Oklahoma City, Oklahoma. He had done considerable investigative work on molds for the government in the state of Tennessee and on botanical aspects of hay fever in the

## IN MEMORIAM

Memphis area. He was a member of the staffs of Baptist Memorial Hospital, John Gaston Hospital and Memphis Eye, Ear, Nose and Throat Hospital. Doctor Goltman was Associate Professor of Medicine at the University of Tennessee. His publications included the following subjects: "Studies in Allergy," "The Mechanism of Migraine," "Unusual Cases of Migraine with Special Reference to Treatment," "Diabetes Mellitus as a Factor in Intractable Asthma," "Migraine," "Allergic Headache."

He is survived by his wife, Helen Hirsch Goltman, and twin daughters, Peggy and Jean.

Doctor Goltman was modest and retiring, sincere, and an enthusiastic member of the College. We mourn his loss.

FRED W. WITTICH

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### HARRY IKER

Mr. Harry Iker, of Chicago, Illinois, died on February 19, 1945, at the age of forty-eight, as a result of coronary disease. He was born in East St. Louis, Illinois, on September 2, 1896. He was actively interested in pharmacy in which he held a degree. In 1932 he began the manufacture of hypo-allergenic encasings and became interested in allergy at the same time. An important part of this work included environmental surveys of patients' homes for physicians.

In 1939 he published the first of his many abstracts of interest to allergists and joined the International Correspondence Club of Allergy. When the American College of Allergists was organized, he was made a charter member and became the only lay Fellow (Associate) in that organization, a distinct honor in itself. He was also a member of the American Pharmaceutical Association and the American Association for the Advancement of Science. At the time of his death he was engaged in the compilation of a reference text concerning items of interest in allergy.

In 1919 he married Rose Weiner. He has two sons in the Armed Forces, Lt. Charles S. Iker of the Infantry, just returned from the Pacific, and Pvt. Howard Iker of the Infantry, now somewhere in Germany.

Harry Iker was a tireless worker whose untimely passing is keenly felt by his many friends in the profession.

MICHAEL ZELLER.

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### Severe Light Hypersensitiveness Cured by Cholecystectomy

(Continued from Page 128)

17. Thurmon, F. M.: Hydroa estivale: A successful treatment. Section on Dermatology, A. M. A., Atlantic City, June 12, 1942.
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19. Urbach, E., with the collaboration of Gottlieb, P. M.: Allergy. New York: Grune and Stratton, 1943.
20. Urbach, E., and Bloech, J.: Hydro vacciniforme, Porphyrinopathie, Hepatopathie. *Wien. klin. Wchnschr.*, 47:527, 1934.
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# News Items

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Dr. John A. Kolmer, Philadelphia, has recently been elected to Honorary Fellowship in the American College of Allergists in recognition of his high attainment in the science of immunology and allergy.

Announcement has been made that Commander M. C. Harris has been released from Naval duty and will resume his practice of allergy at 133 East 58th Street, New York City, beginning April 15, 1945.

The College has just received its second installment for \$500 which is the second grant to the American College of Allergists toward "The Marcelle Research Fund." This fund is being applied to the Fellowship established with the Mayo Foundation under the direction of Dr. Charles F. Code for research in allergy.

Dr. G. Estrada de la Riva, Havana, Cuba, has been promoted to Active fellowship in the College. Doctor de la Riva, who is a member of the Editorial Staff of the ANNALS OF ALLERGY, has been responsible for abstracting the scientific articles which appear in the ANNALS and translating them into Spanish. These abstracts appear in supplement form and are sent to all the Spanish-reading members of the College and other leading allergists in the South and Central American countries and Cuba, who request them.

At the meeting of the Chicago Society of Allergy, held at the Illinois Athletic Club, February 19, Dr. Steven O. Schwartz presented a paper entitled "The Prognostic Significance of Bone Marrow Eosinophiles in Thrombocytopenic Purpura," by invitation, and Dr. Theron Randolph discussed "The Blood Response Following Trial Injection of Food in Allergic Subjects."

At the Seventh Annual Forum, held at Pittsburgh, January 26, Dr. Mary Loveless received the first Marcelle Award of \$350 for her contributions on the role of the thermostabile antibody when determining the clinical response in hay fever. Dr. Charles F. Code, of the Mayo Foundation, received the second Marcelle Award of \$150 on the mechanism of anaphylactic and allergic reactions with an evaluation of the role of histamine in their production. Dr. Arnold Rich and his associates, of Johns Hopkins Medical School, received honorable mention for their studies on serum sickness and periarteritis nodosa. Dr. Frank Simon, of Louisville, also received honorable mention for his observations on human dander in relation to allergy. Dr. Milton J. Rosenau, Professor of Epidemiology, University of North Carolina, received the annual gold medal.

On March 8, at the Annual Doctors' and Wives' Banquet, sponsored by the Spokane County Medical Society, Spokane, Washington, Dr. Herbert J. Rinkel of Kansas City presented "The Etiology of Hay Fever" in Kodachrome stills, following which he presented his outstanding color film "The Symphony of the Seasons." On March 9, at a luncheon meeting of the Society, he discussed "The Diagnostic Problem in Seasonal Hay Fever," and at an evening meeting the same date he presented "Food Allergy."

On March 12, at Vancouver, Washington, Doctor Rinkel presented a combined lecture on "Hay Fever" and "Food Allergy" before the Vancouver County Medical Society.

## NEWS ITEMS

On March 18, he spoke before the Pueblo, Colorado, physicians and their guests concerning "The Treatment of Seasonal Hay Fever" and "The Nature and Mechanism of Food Allergy."

The Southwest Allergy Forum met April 9 and 10 at the Jung Hotel, New Orleans. Although owing to war restrictions the registration was necessarily limited, there was no lack of enthusiasm, and the traditional Southern hospitality promoted informal cordial fellowship.

There were numerous round-table discussions on all phases of allergy, formal presentations of papers and luncheon discussions of timely topics in which anyone could participate.

Among the speakers were Dr. Albert V. Stoesser, who presented the experiences of his staff with "Status Asthmaticus and Pitressin Therapy"; Dr. Coyne Campbell, who gave a most interesting paper on "A Brief Critique of Psychosomatics" in which allergic problems are discussed; Dr. Herbert J. Rinkel, who presented "Migraine"; Dr. Louis Brunsting, who presented "Dermatology as Related to Allergy," and Dr. William F. Petersen, who gave a fascinating talk on "Weather as It Affects the Normal and the Allergic Individual." Doctor Petersen was also guest speaker at the Monday evening dinner.

The leaders of round tables were: Drs. Henry D. Ogden, Jonathan Forman, Homer E. Prince, Fred W. Wittich and L. O. Dutton.

Dr. Ralph Bowen was chairman of the Executive Committee, and Dr. B. G. Efron, chairman of the Committee on Arrangements.

### INSTRUCTIONAL COURSES AVAILABLE

Sets of the complete intensive instructional courses covering all phases of important allergic diseases, presented at St. Louis, November 4 to 8, inclusive, are now available. They include comprehensive outlines and lectures including tables, figures, diets, prescriptions, etc., with space for additional notes.

Subjects and authors are listed below:

- Dermatologic Allergy—Rudolf L. Baer, M.D., New York, N. Y.
- The Physiologic and Immunologic Aspects of Allergy (Illus.)—F. W. Wittich, M.D., Minneapolis, Minn.
- The Diagnosis and Treatment of Allergy of the Nose and Paranasal Sinuses—French K. Hansel, M.D., St. Louis, Mo.
- Some Neurologic and Psychologic Aspects of Allergy—Michael Zeller, M.D., Chicago, Ill.
- Food and Digestive Allergy (Illus.)—Herbert J. Rinkel, M.D., Kansas City, Mo.
- Allergy of the Central Nervous System—T. Wood Clarke, M.D., Utica, N. Y.
- Drug Allergy—Jonathan Forman, M.D., Columbus, Ohio.
- Pediatric Allergy—Ralph Bowen, M.D., Houston, Texas.
- Allergy Elimination Diets for Children, Albert V. Stoesser, M.D., Minneapolis, Minn.
- Mold Allergy (Illus.)—Homer E. Prince, M.D., Houston, Texas.
- Bronchial Asthma—Leon Unger, M.D., Chicago, Ill.
- Physical Allergy—Cecil M. Kohn, M.D., Kansas City, Mo.

The price of the complete set is \$3. Please mail your check with your order.

AMERICAN COLLEGE OF ALLERGISTS  
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# BOOK REVIEWS

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**BRONCHIAL ASTHMA.** By Leon Unger, M.D., Assistant Professor of Medicine, Northwestern University Medical School, Chicago. Introduction by Morris Fishbein, M.D., Editor, Journal of the American Medical Association. 724 pages. 126 figures. One color plate. Price \$9.00. Springfield: Charles C. Thomas, 1945

The book is clearly written for the medical student, general practitioner, specialist and patient and is the most complete single text on bronchial asthma at the present time. The text is divided into three sections. A clinical section comprises by far the greater part of the book. This is followed by a laboratory section and an appendix.

The clinical section contains seventeen chapters. The etiology, diagnosis and treatment of bronchial asthma are emphasized. The author's long years of teaching and extensive clinical practice have particularly fitted him to write a sound textbook on the subject. Theoretical considerations are omitted, without sacrificing the known principles of allergic diseases. Prevention of asthma in children is adequately discussed, as well as an important "Military" chapter, which will assist in the selection and rejection of allergic individuals and in treating those already in the Service.

The laboratory section is devoted to the technique of preparing extracts used for diagnosis and treatment, the technique of pollen and mold counts and special procedures.

The appendix lists the sources of allergens and instructions regarding diets and avoidance of house dust and other excitants. There are detailed instructions for patients which are of considerable practical value, with an alphabetically arranged list of patent medicines for the treatment of asthma, most of which have been analyzed by the Bureau of Investigation of the American Medical Association, and the individual references are noted.

Throughout the book, it is refreshing to see unbiased references and the omission of unimportant assertions of priorities and without belittling fundamental concepts of our present-day knowledge of the allergic reactions, which is manifest in some of our recent textbooks on the subject.

The student, practitioner and specialist will find himself referring to this book more and more.

F.W.W.

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**THE 1944 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY.** By Marion B. Sulzberger, M.D. and Rudolf L. Baer, M.D. 544 pages. 75 illustrations. Price \$3.00. Chicago: The Year Book Publishers, 1944.

In line with WPB restrictions, the publishers continue the same format as the 1943 Year Book. It is a compact handbook, durably bound; the illustrations are clear, and the size of the print for the text and references make it very easy reading.

This book just off the press is packed with 147 new treatments and new proved therapeutic ideas, with additional diagnostic procedures. The unusual experience of the authors with the many skin problems encountered in Military life is incorporated in this volume with up-to-date guidance to more than 150 disease conditions. It is a combination of the clinical findings of dermatologic processes the past twelve months with a critique of nearly 400 leading articles selected from eighty-one clinical publications of this country and thirteen other countries. All positive advances are included with expertly selected illustrations. The information is so arranged that it can be very easily assimilated and easily referred to.

Penicillin therapy of syphilis, sulpha therapy of skin diseases, prophylaxis and

treatment of chancroid, technique of low voltage x-ray therapy of five types of skin lesions, the practical details of industrial, Military, and Naval dermatology, burns therapy and the Navy's new five-hour treatment for scabies are just a few practical points selected from this Year Book. No dermatologic condition seems to have escaped ample consideration by the authors. The formalin treatment of warts, the differentiation of benign and malignant moles, important advances in immunology of dermatologic, venereal and other infectious diseases are adequately presented. The authors include a complete practical guide for skin tests, including patch tests, allergens for patch testing, scratch tests and the intracutaneous test. There are tables of common eczematogenic allergens and common urticariogenic allergens for differential diagnostic scratch testing together with an evaluation of tests. Improved prescriptions and dermatologic therapy in the tropics receive special attention. All of these make this compact manual of skin diseases an extremely useful ready reference for any doctor's office. F.W.W.

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**A MANUAL OF ALLERGY LECTURES FOR NURSES.** By James A. Mansmann, M.D. 32 pages, with outlines, figures and space for notes. Price, 75 cents. Pittsburgh: University of Pittsburgh Bookstore, December, 1942.

The author is lecturer in allergy at St. Francis, Pittsburgh, and Homestead Hospital Nursing School. He is instructor in allergy at the University of Pittsburgh Medical School. Doctor Mansmann's experience in teaching nurses in this specialty qualifies him to prepare an authoritative Manual which is a comprehensive outline of accepted routine procedures in the diagnostic approach and management of allergic diseases to be encountered by nurses during their training and when in private practice.

It is an excellent manual, designed for the nurse with a knowledge of the medical basic sciences and attempts to correct the objections and difficulties of following a course of lectures without any text.

The Manual covers seven to ten hourly lectures and is augmented by demonstrations of skin testing, pollen grains and counts, "dust free" bedrooms and other avoidance and elimination measures. The author assumes that the nurse has had very little contact with this specialty and in all probability an incorrect knowledge gathered from lay sources. Doctor Mansmann prepared the Manual, "hoping the nurse in the future can give the allergic patient intelligent care and helpful suggestions. The allergic patient often depends upon the nurse for correct information." He has succeeded in presenting the essentials for this important instruction so that any lecturer on allergy to nurses will find it of valuable assistance. F.W.W.

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**ESSENTIALS OF ALLERGY.** By Leo H. Criepp, M.D., Assistant Professor of Medicine and Lecturer in Immunology, School of Medicine, University of Pittsburgh; Consultant in Allergy Medical Service of the U. S. Veterans Administration, with a foreword by Robert A. Cooke, M.D., Chairman, Committee on Education, American Academy of Allergy. 381 pages. 42 illustrations. 1 color plate. Price \$5.00. Philadelphia: J. B. Lippincott Co., 1945.

The author, with extensive experience in the teaching of immunology and allergy, is particularly fitted to prepare a manual on allergy for the medical student and for the general practitioner.

There are seventeen chapters covering the various phases of allergy, including the diagnosis and treatment of the various allergic diseases, with a special chapter on allergy in children and a final chapter describing the various diagnostic skin tests. The excellent bibliographies of available material following each chapter indicate the thoroughness with which the author has prepared the manual. In the main, the author adheres to the orthodox teaching of allergy.

## BOOK REVIEWS

The manual is clear and concise. It is excellent for the student of allergy during his undergraduate course, as well as for the general practitioner. F.W.W.

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OUTLINE OF THE AMINO ACIDS AND PROTEINS. By Melville Sahyun, M.A., Ph.D., 251 pages. Numerous illustrations and figures. Price \$4.00. New York: Reinhold Publishing Corporation, 1944

The editor, Vice President and Director of Research, Frederick Stearns and Company, was assisted by twelve contributing authors who hold prominent teaching positions in the departments of Biochemistry of leading medical schools in the United States. There is a foreword by Carl L. A. Schmidt, of the Department of Biochemistry of the University of California.

The authors have succeeded in simplifying in one easily read volume the essentials of the chemistry and biochemistry of amino acids and proteins. They intentionally refrained from the controversial aspects of this difficult subject, but cite references to larger treatises dealing with protein chemical structure, their relationship to immunologic reactions, theories of denaturation, detoxication and other theoretical aspects.

There are eleven chapters, each leading with a photograph of a pioneer who has made fundamental contributions to this important subject. These are accompanied by a brief account of the development of the chemistry and behavior of the proteins and amino acids. Both industry and medicine have awakened to the great importance of proteins and amino acids. Each chapter is followed by a very complete bibliography. There is also a list of general references.

The book furnishes excellent basic knowledge necessary for a clearer concept of the metabolism and functions of the amino acids and for a clearer understanding of their nutritional significance. The last chapter deals with amino acids and proteins in nutrition with a classification of the amino acids with respect to their growth effects, as well as a list of the minimum amount of each essential amino acid necessary to support normal growth when known essentials are included in the food. With our recent knowledge of the important role which globulins play in antibody formation, the chapter on "Relation of Amino Acids and Their Derivatives to Immunity" becomes of special interest to immunologists and allergists.

The book furnishes excellent basic knowledge to the student of the subject as well as the physician in practice. F.W.W.

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CLINICAL ACTIONS OF ETHYLNORSUPRARENIN (Butanefrine) M. L. Tainter, M.D., W. M. Cameron, M.D., L. J. Whitsell, M.D., and M. M. Hartman, M.D. J. Pharmacol. & Experimental Therapeutics, 81:269 (July), 1944.

Ethylorsuprarenin, a new companion drug to epinephrine, has been tried in acute and chronic asthma in patients ranging from three to sixty-four years. Chemically it is 1-(3, 4 dihydroxyphenyl)-2-amino-1-butanol, a colorless, odorless, crystalline powder with a bitter taste, readily soluble in water. Administration was effected subcutaneously, intramuscularly and intravenously. The pressor effects of epinephrine were absent, the diastolic pressure actually being lowered, and the excitant effects on the central nervous system were absent or minimal. Bronchi were effectively relaxed. Doses ranged from 0.2 to 2 mgm. Compared to epinephrine, there was less nausea and vomiting in children and no precordial pain in the older age groups with cardiovascular disease. In general, tremor, nervousness and excitement were either absent or less pronounced than with epinephrine. 50 to 100 per cent larger doses than with epinephrine were required to produce comparable relief. M.M.H.

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NOTE: Ethylorsuprarenin has been referred to as Butafrine and may be again in the future.

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## A BRIEF CRITIQUE OF PSYCHOSOMATICS

COYNE H. CAMPBELL, M.D., F.A.C.P.†

Oklahoma City, Oklahoma

"Man is said to be a compound of soul and body. However proper this language may be in religion, it is not so in medicine. He is, in the eye of a physician, a single and indivisible being, for so intimately united are his soul and body that one cannot be moved without the other. The actions of the former upon the latter are numerous and important. They are causes of many diseases; and if properly directed, they may easily be made to afford many useful remedies. . . .

"I am aware, gentlemen, that the science which I am now recommending to you is an unpopular one, and that it is often treated as chimerical and uncertain. While it bore the name of metaphysics, and consisted only of words without ideas, of definitions of nonentities, and of controversies and the ubiquity and other properties of spirit and space, it deserved no quarter from the rational part of mankind; but the science I am speaking of is as real as any of the sciences that treat upon matter, and more certain and perfect than most of them. As a proof of this I need only call your attention to the innumerable changes that have taken place in the theories of every branch of what is called physical science, and to the improvements which have taken place in each of them within the last two thousand years. Very different is the state of ——— the science of the mind. Most of the leading opinions and observations of Locke, Condillac, Hartley, and Reid may be found in the writings of Aristotle and Plato. . . . The reason of this certainty and near approach to perfection is obvious. The mind is the same now that it was in the time of those illustrious Greek philosophers, and, of course exhibits the same phenomena in all of its operations to the moderns that it did to them."

THESE excerpts from an introductory lecture to medical students given in 1805 by Benjamin Rush<sup>10</sup>, a teacher of general medicine, illustrates that psychological and philosophical psychiatry has undergone no changes in essential content for many years.

However, under the impetus of magical thinking by clinicians of the psychoanalytic school, physicians have been roused, as a matter of defense, from a lethargic attitude toward the importance of domestic, moral, social, and other personal components as concomitants or etiological factors of disease, to an awareness that acknowledgment at least must be made that the physicians "knew it all the time."

<sup>10</sup>Presented at the Southwest Allergy Forum, New Orleans, April 9, 1945.

†Associate Fellow, American College of Allergists.

It is questionable that modern psychological psychiatry is actually more "modern," or has added any pertinent information to its body of knowledge for many years.

Draper<sup>1</sup> has expressed this fact in a recent article:

"If we examine closely the structure of organismic unity which doctors nowadays seem to be striving so hard to preserve for the individual, we may find perhaps that its division resides in a, contemporary medical attitude and not within the animal at all."

And again:

"In our correct professional phrasing, we are by now, no doubt inexorably committed to the word "psychosomatic." The precariousness of the term, however, lies in the fact that its hoped for symbolic connotation of unity may be lost in the false belief that two separate parts in man actually do exist. The only way man has been able to deal with the imponderable forces which he has sensed to be present is by abstract words or symbols. There is, however, a peril in this process, the danger that the possible, wished for, or probable reality for which a given abstraction stands may be obscured by the poignant connotation of the symbol itself, which then takes on the fixed nature of reality."

The term "psychosomatic medicine" is a very unfortunate addition to our unscientific semantics. Loose usage of the term is a threat to modern medical education. It would channelize potentialities and curb the natural efforts of mankind toward better understanding of illnesses that do not belong to the realm of medicine per se. There is no such entity as "psychosomatic medicine" any more than there is "psychosomatic sociology," "psychosomatic philosophy," "psychosomatic politics," or "psychosomatic mysticism."

There are no ontogenetic influences that possess potentialities of producing a reactive organic response from the phylogenetic pattern of an organism so as to characterize the response as being something on the order of a clinical syndrome which should be placed in the category of a psychiatric disability.

It is not within the professional realm of the physician to bear the burden of the connotations involved in the tenets of "psychosomatic medicine." All illnesses that may be the result of emotional conflicts are on a reality basis *to the sufferer*.

It is important that the physician continue his traditional orientation toward humanity and that he realize that current environmental factors responsible for the production of symptoms do not belong in his specific domain. For some reason, the physician is always a specialist in his own way. He is first a physician, second, a politician, gentleman farmer, et cetera, and if he lets the latter interests become too dominant, he no longer is really a qualified physician. The physician was then, is now, and shall be afterwards, a person who attends primarily to disturbances of the "physic."

This does not mean that he should not be a counsellor, or that he should ignore emotional problems in his patient. He should be informed of them, and advice should be given the patient regarding changes that might help, but the major proportion of symptoms that occur as the result of personal relationships involve a moral conflict. The physician-priest relationship was severed gradually many years ago. It would be hazardous for the physician to assume the responsibility of moral guidance, especially since he severed relationship with the priest, and not vice versa.

Advice regarding activities of the patient as to unhygienic attitudes are in order, but the assumption of the role of moral interpreter, with ritualistic components, as manifested by some psychiatric techniques, is not of teleological therapeutic value.

The physician who has patients with reality conflicts that produce allergic or other symptoms may deal with the problem to the best of his ability, but the patient's neighbor who is not professionally trained in anything, might, and often does indulge in counselling, solicited by the patient, with the materialization of excellent results.

There is no academic training that would be apropos. There is no educational program that would be effective so far as "psychogenic" allergic symptoms are concerned; because such a program would be a symptom tantamount to, or worse than the psychogenic allergic manifestations in those people so constituted to react in such a way.

Indulgence in rationalizations of mother, father, sister, brother, grandmother, grandfather, aunt, uncle and cousin relationships as the etiological basis of any chronic ailment is only an indication of a psychiatrist, psychologist, preacher, or like animal in trouble himself.

The herd instinct is a biological expression, not of protoplasm, but of many protoplasms that make up life. Current attitudes would indicate the inevitability of a temporary internationalism, but there is no reason to believe that the amazing modern inventions will alter the cycle of fundamental biological processes.

The psychological aspects of allergy may be dealt with by the allergist much as such problems that have existed and have confronted the family physician for ages. The "psychic" component of the autonomic nervous system disturbances is still in the realm of that wherewithal in which the unknown continues to be the unknown.

Shock therapy in the affective psychoses and in certain types of schizophrenic reactions has effected striking symptomatic improvement. It is likely that scientific studies enacted upon the basis of these results will some day give us enlightenment regarding these most malignant and serious disorders.

The results of prefrontal lobotomy on some special cases is another indication of latent scientific progress in that branch of psychiatry.

Much time could be consumed in the elaboration upon the thesis of



Benjamin Rush, in which he was of the opinion that Plato and Aristotle had fairly well exhausted the fountain of knowledge so far as the human "mind" was concerned.

During the latter part of the 19th century and the first part of this century a very potent and somewhat prolific school of magical thinking came into existence. This school of dogmatists was founded by Sigmund Freud, who became aware of the fact that physicians were not sufficiently cognizant of the importance of reality factors of a personal nature on the influence and production of certain disorders. He did not announce the discovery as such, but instead, created a term, "unconscious," and endeavored to place a premium upon this category. The term was "catchy," and as a result, psychiatrists who supposedly have acquired special ability to deal with this mystical something, have, in the opinion of many, become magically bestowed with unusual conditional abilities. However, now, really, it is believed by most that physicians "knew it all the time."

An elaborate system of "neologisms" has evolved from this school of magic. Examples are: superego, id, ego, repression, sublimation, displacement, oedipus complex, castration complex, penis envy, anal sadism, death instinct, identification, ambivalence, pleasure principle, lay analyses, analysand, transference, counter-transference, polymorphous perversion, passive feminine traits, and dream interpretation. There are many others.

The psychiatrist, from about 1920 on, was something of an outcast, or at least a very "unfortunate creature" unless he had become subjected to the ritual of psychoanalytic training. In the opinion of the psychoanalyst, no person was capable of understanding the psychiatric disorders unless he had been "analyzed" by a qualified training analyst who had met the requirements consisting of a careful scrutiny of the dogmatists.

It is interesting that such a furor occurred, after the founder of the psychoanalytic "school" became aware of emotional factors in the production of illness. Actually, the furor came about as the result of Freud's elaborate delusional system, developed in the effort to explain many very simple phenomena.

The rationalizations and exploitations of the psychoanalysts in the treatment of emotional problems is striking. They extended their claims to cures of such conditions as migraine, essential hypertension, eczema, stuttering, transvestism, hay fever, the common cold, asthma, morphine addiction, sexual perversion and even schizophrenia.

It is no wonder that physicians in other fields of work and that lay persons temporarily succumbed to belief and credence in such a marvelous "psychology." However, there is no doubt but that psychoanalytic technique has never cured a single case of the above-mentioned disorders.

The peripatetic philosophers of ancient Greece would throw both hands up, shake their heads, and walk away if permitted the opportunity of listening to the exchange of words during a psychoanalytic session between the "analyst" and the patient.

There was a "devil neurosis"<sup>4</sup> in the 17th century, but, undoubtedly wheals, eczema, asthma, hay fever, migraine, and blushing, and goose flesh all existed at that time.

There was the case of little Hans<sup>5</sup> who was afraid of horses in 1905, but there are many cases of little Johnnies who are afraid of automobiles and airplanes today.

Freud's explanation of little Hans' fear was that he was afraid of horses because of his incestuous wishes that he had toward mother. The horse was a symbol of father. This is only one example of the innumerable magical explanations of phenomena offered by the psychoanalysts. Modern studies have objectified magical thinking of primitive people. The dogma of psychoanalysis should likewise be objectified.

Lewis<sup>8</sup>, in "Review of Psychiatric Progress 1944," considers Hellier's<sup>7</sup> discussion of dermatologic entities with emphasis upon psychosomatic components as being an important step. Hellier states that many cases of eczema, rosacea, falling hair, lichen planus, hyperidrosis, and warts have a predominance of psychogenic origin. He is of the opinion, however, that these reactions occur only in hypersensitive skins that overreact.

Is it remarkable that one would blush, if one had a tendency to blush, when confronted with a situation that caused blushing? Is it remarkable or even more than ordinary if one's skin has a tendency to epithelialization, that it epithelializes when subjected to epithelializing stimuli?

An example of influence of psychoanalytic thinking occurs in Hellier's explanation of rosacea that occurred in a spinster after her father's death. She sat up with him almost constantly for six weeks before his death. He then died. She developed rosacea which was supposedly a symbolic expression of shame (blushing) because of her guilt over her unconscious wish that her father would die. Is it possible that fatigue of six weeks' constant attendance on her father could have played any part in this skin disturbance? The patient got well after Hellier pointed out her unconscious guilt (according to him)—but she also undoubtedly got a long-needed rest.

Dunbar<sup>2</sup> cites many cases in which she contends that fractures, hypertension, coronary disease, arthritis, and almost every type of allergic disorders have specific psychic components.

French<sup>3</sup>, upon the basis of a study of a few cases of asthma, has concluded that the asthmatic-attack is precipitated by an external situation in which there is a threatened loss of security relative to a mother figure. The asthmatic wheeze to him is on the order of a stifled cry. In his cases he found that the parents overprotected the child to hide their guilt over an inner desire not to have the child. He recommends to parents, less solicitation of these children, and to the children, a more independent attitude toward the parents.

Wilson<sup>12</sup> believes that hay fever (after his analysis of seven cases) is the result of inadequately repressed olfactory sexual impulses. It has

something to do about man taking the upright position, and the nose getting too far from the ground. His patients were from Victorian families who changed the child's interest from the genitals to body excretions.

Saul<sup>11</sup> states that the common cold, hay fever, and allergy in general are manifestations of suffered intensification and frustration of passive receptive wishes with a strong oral component. Dreams presented by his patients, according to his interpretation, showed strong wishes for help from others. He states that colds would dramatically disappear when the patient acquired insight, or when frustration was alleviated. It is his opinion that colds and hay fever are perhaps closely related if not identical. However, no smears of the nasal mucosa were studied by him on any of his patients.

Fromm-Reichmann<sup>6</sup> has concluded that migraine is caused by repressed hostility toward a loved one in which the patient is not consciously aware of it. She states that it occurs in families who do not permit children to fight each other. The head is chosen as the site of pain because it is a symbol of intellectual rivalry. (If this is not magical thinking, then the primitive who poured water over rocks to produce rain was an intellectual genius!)

It would seem to be the tendency now to place most not understood clinical syndromes into the realm of "psychosomatic disorders."

Lipkin and Sharp<sup>9</sup> supply the following list:

"Cardiovascular neurosis, certain cases of hypertension, Raynaud's hyperventilation syndrome, many cases of asthma, cardiospasm, aerophagia, hyperacidity, acidity, peptic ulcer, pylorospasm, biliary dyskinesias, mucous colitis, spastic and atonic constipation, ulcerative colitis, enteroptosis, urinary frequency, sexual disturbances, menstrual disturbances, neurodermite, urticaria, angioneurotic edema, eczema, certain cases of arthritis, certain types of headache, migraine, anorexia nervosa, and even obesity."

Let us not forget that general paresis was at one time similarly categorized.

Numerous writers have attempted clarification of clinical disorders being emotional, structural, or a mixture of both. Such classifications are essentially very loose and ill-defined.

There are many examples of physiologic reactions to emotional stimuli, and many theorize that these responses over a sufficient period of time will produce irreversible pathology. However, it remains to be proved that the responses that resulted in pathological changes were ever at any time physiological. Hypertension is a good example of this. The hypertension produces alterations in the arteries that became irreversible. But, was the hypertension that produced the arterial changes ever physiological?

There are writers who state that leukocytosis occurs on an emotional basis. Basal metabolic rates supposedly are altered by the emotions. The skin temperature drops in some people when disturbing subjects are discussed.

Treatment suggested by Lipkin consists of suggestion, catharsis, relax-

ation therapy, prescribed exercise, persuasion, psychoanalysis, distributive analysis, and group psychotherapy.

Psychosomatic medicine is being pushed by the psychoanalysts who have ready magical explanations for symptoms that cannot be explained as yet upon physio-pathologico-biological scientific grounds.

It is morbidly amusing to read the psychoanalytic and other psychologic literature pertaining to schizophrenic psychoses written in the pre-shock treatment era. One would really have difficulty in differentiating the patient's "material" from the analyst's "interpretations."

The psychoanalytic technique is nothing more than a relationship between the physician and patient (if the analyst is a physician), in which both the patient and analyst indulge in mutual fantasies toward each other. The procedure finally terminates when they tire of each other or when the patient's funds are exhausted. The pseudotherapeutic results consist of an induced delusional mosaic in the patient. The analyst had the delusions before the procedure was started. It is so to speak something on the order of a folie à deux.

This is not to minimize the influence of conflict situations in the production of allergic and other clinical symptoms. Undoubtedly such phenomena do occur—but they do so just as any added strain, or worry, or other reality situation would aggravate a manifest disease process. This is no new discovery and hardly deserves any special terminology for its description. Psychiatry, the so-called "Cinderella of Medicine," is permitting itself to be overrated. It has its place in medicine, but the dichotomy of mind and body is dangerous to science.

The psychiatrist has no specially pertinent information to impart to the allergist. Every allergist knows, just as every other physician knows, that the physician-patient relationship, as per the Hippocratic Oath implies that the doctor may make an appraisal of the intimate personal information obtained.

Advice to patients relative to any reality problems or conflicts that might be enhancing his allergic symptoms does not spring from information given through the discovery of a psychiatrist. It is the *sine qua non* of the physician as a part of the art of medicine.

It is important to stress to medical students that a careful history, with special inquiry regarding the possibility of emotional problems, be obtained. Evaluation of the information is not difficult. Errors in interpretation are more likely to occur on the "psychosomatic" rather than the biologic side.

Factors in reality that add to strain in constitutionally predisposed people who suffer with allergic conditions may, theoretically, in some instances provoke an attack. Even this remains to be scientifically proved.

The famous case of Prince is frequently quoted, in which sneezing occurred in a patient with hay fever sensitive to roses when shown a paper rose. This is not pertinent, because it was not shown that the attack of sneezing was an attack of hay fever.

Conditioned reflexes are definite entities and it is normal for one to respond with defense mechanisms to irritating or danger situations. However, what would be proved if a man who was sensitive to ragweed, and who knew what a ragweed looked like, sneezed when confronted with an artificial ragweed that looked like the real McCoy?

Would Prince's patient have sneezed at the artificial rose, had he not known that he was sensitive to roses?

Some practical points are herewith given, not with the idea of being informative, but more as a space filler for the paper.

In the examination of children, to discover the existence of a pertinent emotional problem, careful inquiry should be made into the matter of adjustment between the parents. If the inquiry does not call attention to and aid in the maladjustment, treatment of any sort will only serve to make matters worse.

In the adult in which an emotional conflict is discovered, it is well to determine the nature of the conflict.

Is the problem on a moral basis? e.g., does the patient have an illicit affair? Has he cheated on his income tax report? Has he borrowed money from an opulent relative and deliberately failed to make payments on the debt? Has he been padding his expense account? Has he spread malicious gossip about a competitor? He should be asked very frankly if any moral problems exist. Expression of the fact to the physician may or may not help; but again, attention is called to the fact that such might be a factor in the illness and may bring the matter to a focus in reality and the patient sometimes will take steps to correct the situation.

Is the emotional problem arising out of the person's inadequacy? Frequently such is the case. The patient is aware of the fact, but had not connected it with the presenting symptoms. When such is found to be true, the patient should be frankly told of the situation. Improvement depends upon the ability of the patient to adjust to the passive acceptance of an altered status and changed evaluation of himself. Some cannot make this adjustment. No one actually knows the reason why.

Is the emotional problem just an external situation, incidental, but inevitable, that is really overwhelming because of being a threat to the person's health, security, or other attributes of happiness? If so, nothing can be done until the external situation is altered.

This presentation has been made in the interest of medicine, with the concept that psychiatrists have no more information as to correction of social conflicts than do many other people. It is also presented in the interest of psychiatry to emphasize the above fact.

It is an extremely common, though embarrassing occurrence for the psychiatrist, after introduction, to have the person say, "Oh, you're a psychiatrist! I'm glad to meet you. I've always wanted to be psychoanalyzed. Let's go over here and sit down. I want you to psychoanalyze me right this minute."

Unfortunately, this impression and overestimation of the psychiatrist has become rather prevalent, and I'm afraid that the psychiatrist has unwittingly permitted it to be brought upon himself.

The psychiatrist is just a physician interested in the diagnosis, prognosis, further understanding, and treatment of disorders with clinical symptoms that places the patient in the category of a psychiatric disturbance.

There are no convincing reports in the literature of any allergic patients having received any more relief from psychiatric treatment than should have otherwise occurred from wise counseling with the allergist.

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*Urticaria Following a Dental Silver Filling.* Marcow, H.: Dental Outlook, 31:148, 1944.

The author reports this case of sensitivity to mercury or quicksilver used as dental fillings. The urticaria was present daily with its onset being noted immediately following a visit to the dentist. She experienced complete relief on the removal of all silver fillings. After the removal of each silver filling, there was a flare-up of urticaria for several hours. The contact test with mercury was immediately followed by a large area of urticaria over the test site.

*The Mycotic Flora of the Oral Cavity in Normal and Pathological Conditions.* Ottolenghi, R.: Dental Items, 66:134, 1944.

The author collected samples for culturing from the oral cavities of 100 patients affected with various dental disturbances. These samples were cultured in selective media, with positive findings in ten patients. Identification of the growth was accomplished by its cultural and microscopic characteristics, by hanging drop preparations and by carbohydrate fermentation patterns. The fungi were divided as follows: saccharomyces hominis, monilia (Zeilanica Castellani) (two cases), aspergillus herbariorum, sporotrichum, monilia undetermined (three cases), penicillium glaucum, and saccharomyces glomerolatus.

# EXPERIMENTAL APPROACH TO ORAL TREATMENT OF FOOD ALLERGY

## II. Immunologic Properties of Food Propeptans

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THE first paper in this series dealt with the chemistry of food propeptans. Food propeptans are food digests derived from the individual foods through prolonged digestion with hydrochloric acid and pepsin, followed by some slight additional digestion with trypsin. Thus, these preparations contain all the protein cleavage products such as the proteoses, peptones, subpeptones, simple peptids and amino acids, but no native protein.†

In the present communication—the second in the series—an attempt will be made to describe the immunologic properties of food propeptans.

Today, as is well known, distinction is made between two outstanding methods of anti-allergic treatments: hyposensitization and de-allergization (Urbach and Gottlieb).<sup>10</sup> The term hyposensitization designates the procedure by which the allergic organism is given small quantities of antigen in repeated and usually increasing doses at intervals of one or more days. Subsequent administration of an anaphylactic dose will be tolerated without manifest symptoms, although the lungs (in the lung perfusion test) and the uterus (in the Schultz-Dale test) are still anaphylactic. Therefore, the clinical insensitivity can be explained only on the basis of an excess of free circulating antibodies.

The term de-allergization designates the therapeutic measures by which, through the appropriate administration of antigen, the antibodies are neutralized or otherwise rendered incapable of reacting. In this manner, the principal shock tissues or the entire organism are rendered insensitive for a certain length of time or permanently.

In this paper, animal-experimental evidence will be adduced to demonstrate that propeptans lead to de-allergization—i.e., that propeptan therapy converts the organism from a state characterized by a high antibody titer to one in which the antibody level is normal. However, depending on quantitative and timing conditions, the de-allergization may be partial and temporary, complete but temporary, or complete and lasting.

On the other hand it will be shown that parenteral administration of food proteins while resulting in a clinical state of temporary hyposensi-

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Sequel to "Experimental Approach to Oral Treatment of Food Allergy. 1. Chemistry of Food Propeptans." Erich Urbach, M.D., George Jaggard, B.S., David W. Crisman, V.M.D., *Ann. Allergy*, 2:424, 1944.

\*Associate Fellow, American College of Allergists.

†Food propeptans are in themselves entirely free from protein; however, for reasons stated elsewhere in this paper, glycyrrhiza is added to the propeptans intended for therapeutic use. This saponin contains 1.4 per cent protein nitrogen. Pure food propeptans for analytic or experimental purposes will be supplied by Dalare Associates, 2300 Locust Street, Philadelphia 3, Pa., on request.

tization does not deprive the shock organs of the antibodies, thus rendering the organism clinically sensitive again shortly after the hyposensitization treatment has been stopped.

After reviewing the literature on the antigenicity of the cleavage prod-

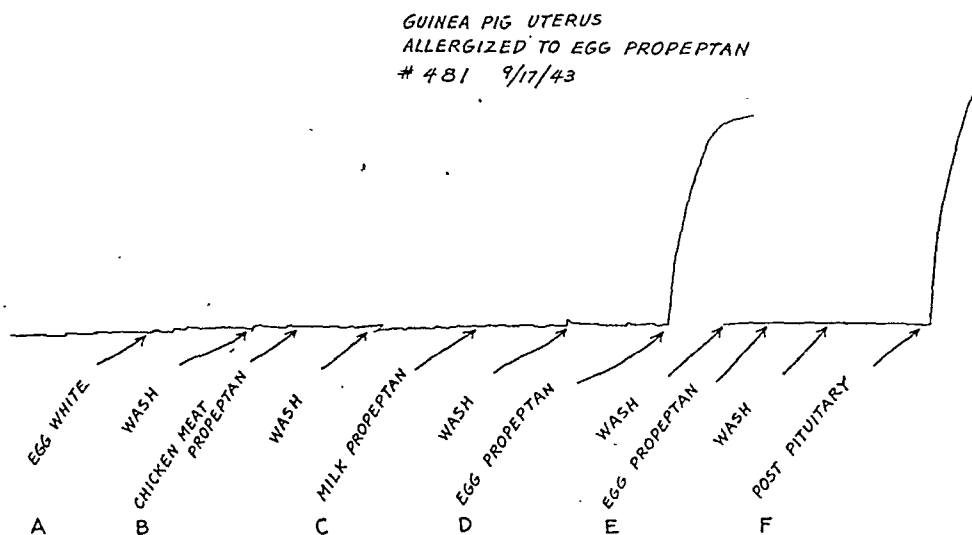


Fig. 1. Schultz-Dale test performed upon the uterus of guinea pig No. 481 allergized to egg propeptan. There was no reaction upon the additional egg white, chicken meat propeptan, or milk propeptan; however, the addition of egg propeptan resulted in a violent reaction. There was no reaction to a second portion of egg propeptan proving that the first reaction was specific for egg white. The final reaction was the result of posterior pituitary extract added as a check on the sensitivity of the uterus.

ucts resulting from the action of enzymes on protein, up to the year 1919, and on the basis of his own experimental work, Fink<sup>3</sup> arrived at the conclusion that it was most unlikely that the proteoses had any antigenic property. However, Landsteiner<sup>5</sup> succeeded in demonstrating that animals sensitized with digestive cleavage products of egg albumin responded to a re-injection of the same substance with characteristic and fatal anaphylactic symptoms. Urbach and Kitamura<sup>5</sup> were able to allergize guinea pigs by means of oral as well as parenteral administration of type-specific propeptans. This was demonstrated both by the anaphylactic experiment and by the Schultz-Dale test on a specifically sensitized uterus. Lastly, Cooke et al.<sup>2</sup> have reported sensitization of guinea pigs to Berna peptone.

All this would seem to establish the fact that the cleavage products of proteins possess anaphylactic properties. Furthermore, the senior author<sup>8</sup> has demonstrated the strict type-specificity of propeptans. The uterus of a guinea pig, sensitized with hen's egg propeptan, responds with contraction to hen's egg propeptan alone, showing no reaction whatsoever to administration of hen's egg white.

The high degree of the specificity is revealed by the fact that even propeptans, derived from hen's meat, fail to elicit any kind of reaction (Fig. 1). The type-specificity of food propeptans, as demonstrated by the



Schultz-Dale test (generally recognized as the most accurate and dependable procedure), conforms perfectly with our experimental findings in man. In this connection, we<sup>8</sup> should like to call attention to the case in which preliminary administration of egg propeptan inhibited the appearance of an allergic eczema when egg white was applied to the eyelids, or of an allergic rhinopathy following the introduction of egg white tampons into the nostrils; yet the appearance of these allergic responses was not inhibited when the patient, believing that she had received egg white propeptan, had in fact been given hen's meat propeptan. Similarly, in a case of asthma due to peas, the patient was able to eat quantities of peas with impunity, provided the specific pea propeptan was taken before the meal; but a severe attack was the result when the same quantity of lentil propeptan was substituted for the pea propeptan, without the patient's knowledge. Many similar instances could be cited from the literature and our own experience.

Thus, clinical observations and experimental findings alike demonstrate the type-specificity of the propeptans; and this would seem to establish the experimental and theoretical grounds for recognizing the value of propeptans in the diagnosis of food allergy. We shall now attempt to present conclusive animal experimental evidence of the therapeutic efficacy of the propeptans.

As is well known, Besredka<sup>1</sup> demonstrated that pre-administration of a given antigen whether subcutaneously, intravenously, intrathecally, rectally or orally affords complete protection against what would otherwise be a fatal dose of allergen. This is the basic principle involved in the procedure known as specific skeptophylaxis. The senior author<sup>13</sup> subsequently succeeded in showing that instead of giving the antigen itself (e.g., egg white), the corresponding propeptan (egg propeptan) may be advantageously used. The great advantage of substituting the type-specific food digest for the food antigen lies in the fact that both in humans and in animals, the degree of hypersensitiveness is not uncommonly so high that even minute quantities of the food in question may bring on very severe anaphylactic symptoms.

In the present study, we performed extensive experimental studies to re-determine conditions under which guinea pigs, sensitized by the intraperitoneal or subcutaneous route can be protected against the effects of a lethal anaphylactic shock-dose by type-specific propeptans administered intravenously or by mouth.

For each experiment, we used twenty virgin guinea pigs, weighing an average of 280 gm. and kept on an acid diet throughout, consisting of 7 gm. of rolled oats, 5 gm. of whole-wheat bran, 10 gm. each of potatoes, beets and hay daily. This is necessary, for animals given a diet of green fodder which is alkalizing are difficult to sensitize (Sulzberger and Mayer<sup>9</sup>). Parenteral allergization to egg white is readily achieved within three weeks by an intraperitoneal or subcutaneous injection of 0.1 c.c. of 50 per cent

egg white in saline. However, if the animals are to be sensitized to milk, meat, spinach, flour and other food proteins, it is advisable to inject 2 c.c. of skimmed milk, beef, flour, et cetera, together with 0.02 c.c. of alum precipitate, subcutaneously. The animals then show a high degree of hypersensitiveness after forty-three to forty-seven days. Needless to say, each individual preparation must be carefully checked to rule out any possible toxic action or tendency to evoke a nonspecific reaction on the uterus in the Schultz-Dale test. A preparation may be classified as nontoxic, when an intravenous injection of 4 c.c. of a 10 per cent digest is tolerated perfectly by the animal. Furthermore, it is necessary to perform preliminary experiments on a number of animals from each group, in order to determine the minimal lethal dose (M.L.D.) required for each series of experiments. The minimal lethal dose varies, depending on the animal's strain and weight, diet and the season.

Sensitization by the oral route is facilitated considerably by the addition of the saponin glycyrrhiza to the food protein. Glycyrrhiza increases the allergizing properties of the antigen manyfold because of better resorption resulting from its action in dissolving intestinal mucus (Urbach<sup>10</sup>). Another way to expedite sensitization is to introduce 1 c.c. of 25 per cent alcohol into the animal's stomach by means of a catheter before administering the allergic food to which the animal is to be sensitized. We have found this method, which was introduced by Hajos<sup>4</sup>, to be highly effective.

#### ORIGINAL EXPERIMENTS

Twenty guinea pigs were allergized by means of an intraperitoneal in-

##### *Experiment 1*

Guinea pig No. 778 allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline. Three weeks later, the following treatment was instituted.

*Treatment.*—Five intravenous injections of Egg Digest\* at ten-minute intervals.

- Injection 1.—Egg Digest representing 1.0 mgs. of Soluble Nitrogen—No reaction
- Injection 2.—Egg Digest representing 2.5 mgs. of Soluble Nitrogen—No reaction
- Injection 3.—Egg Digest representing 5.0 mgs. of Soluble Nitrogen—No reaction
- Injection 4.—Egg Digest representing 10.0 mgs. of Soluble Nitrogen—Slight bristling
- Injection 5.—Egg Digest representing 20.0 mgs. of Soluble Nitrogen—Slight bristling

Three hours after the last injection of Egg Digest one horn of the uterus was removed and a Schultz-Dale test performed.

Schultz-Dale test.—Negative to Egg Digest, strongly positive to egg white (Fig. 2).

Five days later—

*Treatment.*—Intravenous injections of Egg Digest at ten-minute intervals:

- Injection 1.—Egg Digest representing 1.0 mgs. of Soluble Nitrogen—No reaction
- Injection 2.—Egg Digest representing 2.5 mgs. of Soluble Nitrogen—No reaction
- Injection 3.—Egg Digest representing 5.0 mgs. of Soluble Nitrogen—No reaction
- Injection 4.—Egg Digest representing 10.0 mgs. of Soluble Nitrogen—Slight bristling
- Injection 5.—Egg Digest representing 20.0 mgs. of Soluble Nitrogen—Slight bristling

Fifteen minutes later—

Shock dose (2.5 M.L.D.)—Bristling and twitching nose. One hour later, the animal was killed.

*Schultz-Dale test.*—Negative to egg white (Fig. 3).

*Lung perfusion test.*—Positive to egg white (Fig. 4).

\*Regarding the chemical composition of egg digest, see Table II of first paper of this series.<sup>11</sup>

jection of 0.1 c.c. of 50 per cent egg white in saline. After twenty-one days, these animals were so highly hypersensitive that an intravenous injection of 0.5 c.c. of a 0.1 per cent egg white solution led to instantaneous death accompanied by the most severe manifestations of anaphylactic

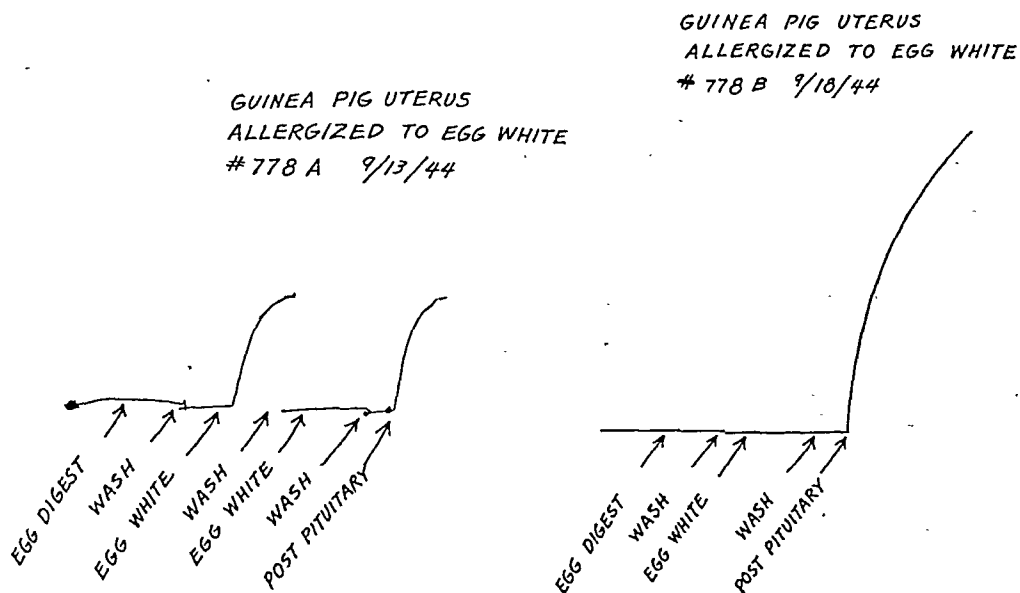


Fig. 2. (left) Schultz-Dale test performed upon the uterus of guinea pig No. 778 allergized to egg white and treated with intravenous skeptophylactic injections of egg digest. (Only one horn of the uterus was removed and the animal was subsequently used in the second part of Experiment I, Fig. 3). There was no reaction upon the addition of egg digest. A violent reaction followed the addition of egg white, indicating the presence of considerable quantities of antibodies. No reaction followed a second addition of egg white, proving that the preceding one was specific. A final addition of posterior pituitary extract was made as a check upon the sensitivity of the uterus.

Fig. 3. (right) Schultz-Dale test performed upon the second uterine horn of guinea pig No. 778 allergized to egg white and treated with intravenous skeptophylactic injections of egg digest followed by intravenous injection of  $2\frac{1}{2}$  minimal shock dose of egg white (same animal as used in Figure 2). There was no reaction upon the addition of egg digest or egg white, indicating the absence of antibodies in the uterus. The posterior pituitary extract was added as a check upon the sensitivity of the uterus.

shock. Therefore, in this group of animals, the minimal lethal dose was 0.50 c.c. of a 0.1 per cent egg white solution.

Guinea pigs previously intraperitoneally allergized to egg white were given mounting doses of egg propeptan intravenously, and one uterine horn of an animal so prepared, removed two hours after the last injection, showed a negative reaction to the egg propeptan, but a positive reaction to the egg white (Fig. 2).

Five days later, when the abdominal wound had healed completely and the animal seemed healthy and was eating normally again, the same pre-treatment schedule was repeated. This time, however, two and one-half times the minimal lethal dose was injected intravenously fifteen minutes

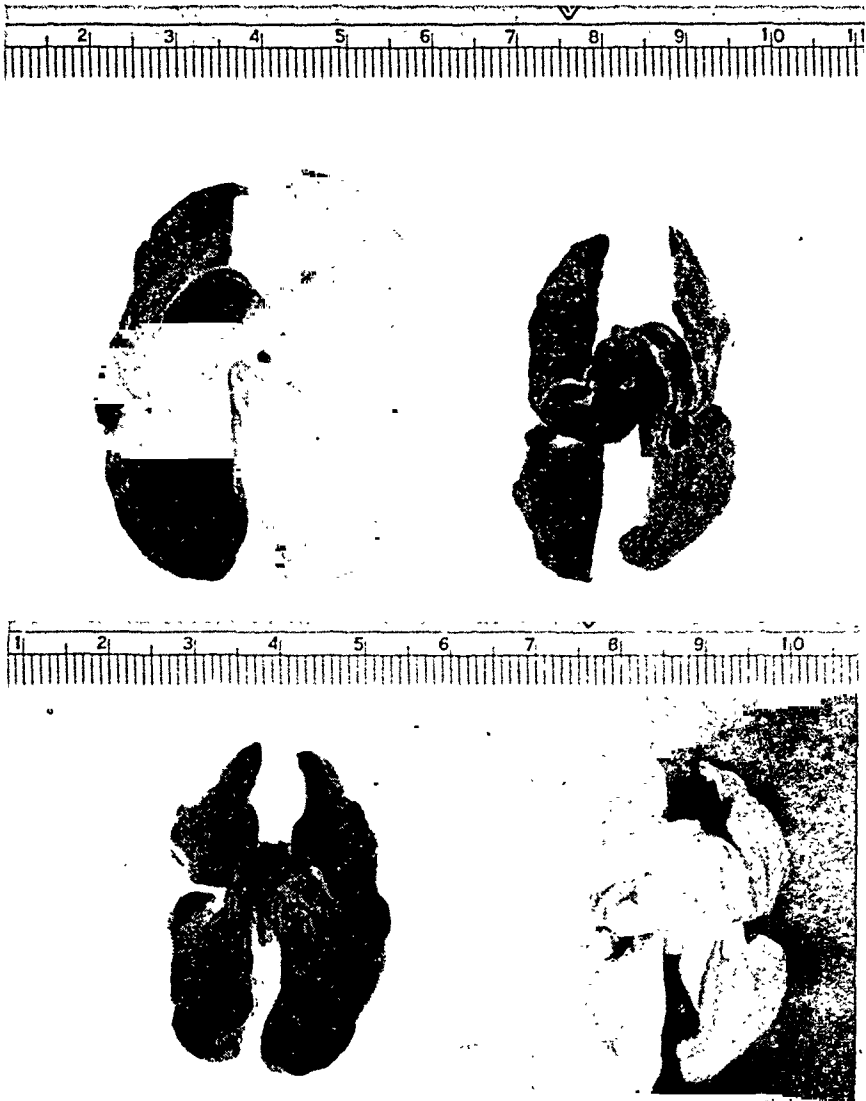


Fig. 4. Lung perfusion test performed upon the lung of guinea pig No. 778 allergized to egg white, treated with intravenous skeptophylactic injections of egg digest and killed *one hour* after surviving  $2\frac{1}{2}$  minimal lethal shock doses of egg white. The lung (*left*) reacted with marked inflation indicating the presence of considerable quantities of antibodies. A control lung of a nonallergized animal of the same weight (*right*) showed negative reaction in the lung perfusion test.

Fig. 5. Lung perfusion test performed upon the lung of guinea pig No. 793 allergized to egg white treated with intravenous skeptophylactic injections of egg digest and killed *six hours* after surviving  $2\frac{1}{2}$  minimal lethal shock doses of egg white. The lung (*left*) showed no inflation, indicating the absence of antibodies. A control lung of a nonallergized animal of the same weight (*right*) showed negative reaction in the lung perfusion test.

after the last injection, but the animal showed no allergic response whatsoever. When the animal was killed by a blow on the head an hour later, and the Schultz-Dale test was performed on the second uterine horn, there was no reaction to egg white (Fig. 3). Evidence that the uterus had not lost its reactivity was given by its strong response to posterior pituitary extract.

While the animal was clinically protected against two and one-half times the minimal lethal dose, and the uterus was found to be free from antibodies, the lung reacted to the lung perfusion test with marked inflation when flooded with egg white solution (Fig. 4). This shows that there was still an abundance of antibodies in the guinea pig's primary shock tissue (the lung is generally regarded to be the shock tissue in these animals). It is to be noted, however, that the animal was killed *one hour* after the injection of the shock dose. When the guinea pig is not killed until *six hours* after administration of the shock dose, the antibodies in the lung are found to be satiated, as shown by a negative lung perfusion test (Fig. 5). The antibodies in the uterus were found to be neutralized in some cases, at this time, while in other animals the presence of antibodies could again be demonstrated.

### Experiment 2

Guinea pig No. 793 allergized to egg white.

Intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline. Three weeks later the following treatment was instituted.

*Treatment.*—Five intravenous injections of Egg Digest at ten-minute intervals.

Injection 1.—Egg Digest representing	1.0 mgs. of Soluble Nitrogen—No reaction
Injection 2.—Egg Digest representing	2.5 mgs. of Soluble Nitrogen—No reaction
Injection 3.—Egg Digest representing	5.0 mgs. of Soluble Nitrogen—No reaction
Injection 4.—Egg Digest representing	10.0 mgs. of Soluble Nitrogen—Bristling
Injection 5.—Egg Digest representing	20.0 mgs. of Soluble Nitrogen—Bristling

Fifteen minutes later—

Shock dose (2.5 M.L.D.)—Bristling

Animal killed six hours later

Schultz-Dale test—Negative

Lung perfusion test—Negative (Fig. 5).

When the animal is not sacrificed until *twelve hours* after administration of two and one-half times the shock dose, both uterus and lung again show positive reactions to egg white. This indicates that the antibody-satiation was only temporary and that, in other words, the neutralization is over-compensated by the presence of newly formed antibodies in the shock organs.

The first part of Experiment 1 has already shown that the mere administration of mounting doses of propeptans, intravenously, does not afford any protective action whatsoever. The intravenous injection of the food digest must be followed by an injection of the given food protein to produce the phenomenon of (temporary) de-allergization, as evidenced by clinical insensitiveness to two and one-half times the minimal lethal dose and by the negative results of the Schultz-Dale test, and the lung perfusion test.

This de-allergization takes place in the uterus a short time (one hour) after administration of a multiple minimal lethal dose and continues some five or six hours. In the lung, however, de-allergization does not take place until six hours after the injection but is still demonstrable nine hours after the injection. The possible explanation may be that it requires more time to satiate all the antibodies in the lung because the lung is, of course, a considerably larger organ, and thus, contains a greater number of antibodies to begin with, and, also, because the lung is the primary shock organ in the guinea pig.

The reasons for the unreactivity on the part of the highly sensitized uterus and lung after pre-administration of type-specific propeptans are not, as yet, fully understood. The senior author<sup>12</sup> has expressed the opinion that the action of the propeptans are based on the principle of skeptophylaxis (anti-anaphylaxis)—i.e., the concept that administration of food digest brings on micro-shocks which are strong enough to neutralize temporarily the available supply of antibodies. This results in what is known as a negative, or anergic, phase in which the newly administered antigen fails to encounter antibodies, and, therefore, cannot evoke an anaphylactic reaction. After twelve hours, however, this state of neutralization comes to an end, as shown by the positive Schultz-Dale test and lung perfusion test. Clinically, on the other hand, the animal is still protected against two and one-half times the minimal lethal dose.

Other immunologic conditions are achieved when the skeptophylactic treatment of the animals is carried out by intravenous administration of gradually mounting doses of minute quantities of the native (i.e. undigested) food protein, as shown in Experiment 3.

### *Experiment 3*

Guinea pig No. 791 allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline.

Three weeks later the following treatment was instituted.

*Treatment.*—A series of increasing doses of egg white at ten-minute intervals (M.L.D.: 0.25 c.c. of 0.1 per cent egg white solution).

Injection 1.	—0.1	c.c. of 0.01% egg white	—No reaction
Injection 2.	—0.25	c.c. of 0.01% egg white	—No reaction
Injection 3.	—0.50	c.c. of 0.01% egg white	—No reaction
Injection 4.	—1.00	c.c. of 0.01% egg white	—No reaction
Injection 5.	—0.10	c.c. of 0.10% egg white	—No reaction
Injection 6.	—0.20	c.c. of 0.10% egg white	—Bristling
Injection 7.	—0.50	c.c. of 0.10% egg white	—Bristling

Animal killed three hours after the last injection and a Schultz-Dale test and a lung perfusion test performed.

Schultz-Dale test—Positive

Lung perfusion test—Positive

This skeptophylactic pre-treatment also succeeds in protecting a certain percentage of the animals against a double minimal lethal dose, but when the animals are sacrificed one, two, three, six, twelve hours later, the uterus and lung show strong reactions to egg protein (except for a few cases in which the lung perfusion test was negative six hours after this injection series). Thus, repeated injections of undigested protein cannot

produce even temporary de-allergization, immunologically, speaking. In this connection, it is important to note that these experiments must be performed most cautiously, with much smaller doses than when protein digests are used, for the danger of evoking a fatal anaphylactic shock in

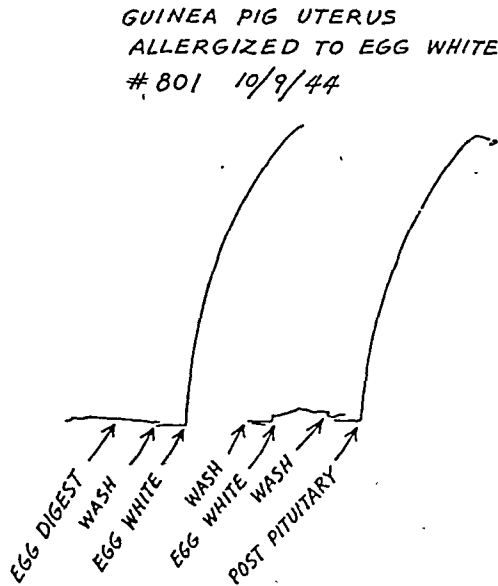


Fig. 6. Schultz-Dale test performed upon the uterus of a guinea pig No. 801 allergized to egg white and treated with intravenous injections of a series of increasing doses of egg white at two-day intervals (method of hyposensitization). The animal was killed *six hours* after the last injection. There was no reaction upon the addition of egg digest. A violent reaction followed the addition of egg white indicating the presence of considerable quantities of antibodies. No reaction followed a second addition of egg white, proving that the preceding reaction was specific. A final addition of posterior pituitary extract was made as a check upon the sensitivity of the uterus.

the guinea pig is far greater when native protein is injected. Yet the seventh injected dose (0.50 c.c. of 0.1 per cent egg white) contains only 0.01 mg. of soluble nitrogen, as compared with the 20 mg. of soluble nitrogen in the egg digest which can be given with impunity at the fifth injected dose. Apparently, even such minute quantities of native protein are too great to elicit micro-shocks, which alone are able to neutralize the antibodies. Thus, these experiments also demonstrate that the food protein digests are superior to the native food proteins, from the therapeutic viewpoint.

This becomes even more clearly apparent when the native food protein is injected in gradually mounting doses every twenty-four to forty-eight hours (method of hyposensitization), instead of intervals of ten or twenty minutes. In this manner, the animals can be protected against a quadruple minimal lethal dose. However, even after eight such injections, the Schultz-Dale test and the lung perfusion test are still strongly positive, showing that this method does not reduce the number of antibodies.

*Experiment 4*

Guinea pig No. 786 allergized to egg white.

Intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline. Three weeks later the following treatment was instituted.

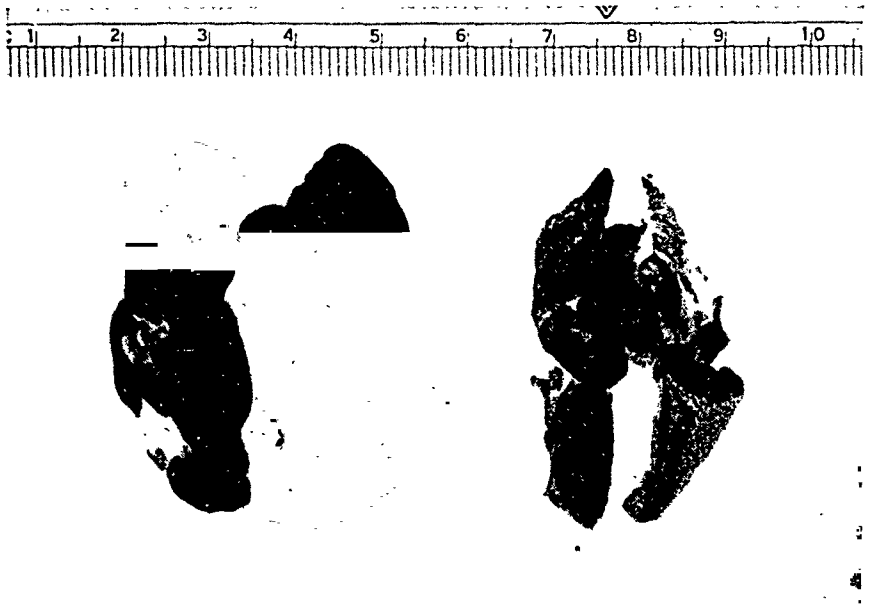


Fig. 7. Lung perfusion test performed upon the lung of guinea pig No. 801 allergized to egg white and treated with intravenous injections of a series of increasing doses of egg white at two-day intervals (method of hypsensitization). The animal was killed six hours after the last injection. The lung (left) showed marked inflation, indicating that the number of antibodies were not reduced. A control lung of the nonallergized animal of the same weight (right) showed a negative reaction in the lung perfusion test.

*Treatment.*—A series of daily increasing doses of egg white intravenously (1 M.L.D.—0.5 c.c. of 0.1 per cent egg white solution)

9/14/44—0.1 c.c. of 0.1% egg white—No reaction  
 9/15/44—0.2 c.c. of 0.1% egg white—No reaction  
 9/16/44—0.5 c.c. of 0.1% egg white—No reaction  
 9/17/44—0.5 c.c. of 0.1% egg white—No reaction  
 9/18/44—0.5 c.c. of 0.1% egg white—No reaction  
 9/19/44—1.0 c.c. of 0.1% egg white—No reaction  
 9/20/44—1.0 c.c. of 0.1% egg white—No reaction  
 9/21/44—0.2 c.c. of 1.0% egg white—No reaction

Animal killed three hours after the last injection.

Schultz-Dale test—Positive

Lung perfusion test—Positive

*Experiment 5*

Guinea pig No. 801 allergized to egg white.

Intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline. Three weeks later the following treatment was instituted.

*Treatment.*—A series of increasing doses of egg white administered intravenously at two-day intervals.

9/29/44—0.50 c.c. of 0.01% egg white—No reaction  
 10/ 1/44—0.10 c.c. of 0.10% egg white—No reaction  
 10/ 3/44—0.25 c.c. of 0.1 % egg white—Bristling  
 10/ 5/44—0.25 c.c. of 0.1 % egg white—No reaction  
 10/ 7/44—0.50 c.c. of 0.1 % egg white—Bristling  
 10/ 9/44—1.00 c.c. of 0.1 % egg white—No reaction

Animal killed six hours after the last injection.

Schultz-Dale test—Positive (Fig. 6)

Lung perfusion test—Positive (Fig. 7)



Hitherto, the discussion has been confined to conditions in animals that (1) had been allergized parenterally, (2) were given for protection the

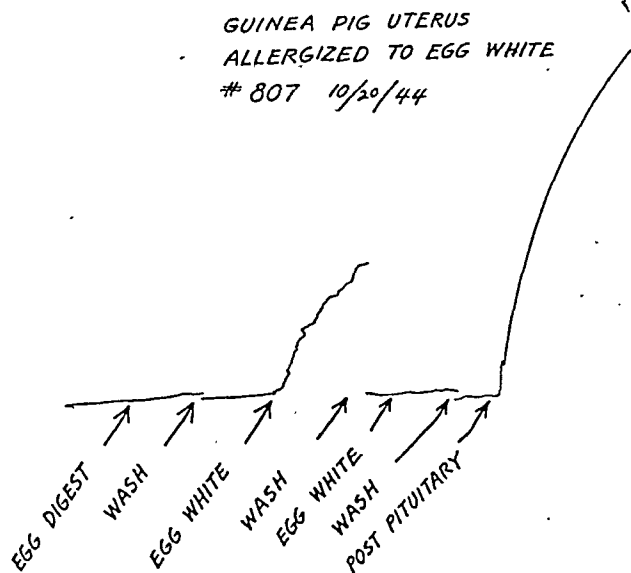


Fig. 8. Schultz-Dale test performed upon the uterus of a guinea pig No. 807 allergized to egg white, treated orally with egg digest followed by intravenous injections of multiple shock doses of egg white (three treatments). The animal was killed *six hours* after the last shock dose. There was no reaction upon the addition of egg digest. An attenuated positive reaction followed the addition of egg white, indicating partial neutralization of the antibodies. No reaction followed a second addition of egg white, proving that the preceding reaction was specific. A final addition of posterior pituitary extract was made as a check upon the sensitivity of the uterus.

food digest intravenously, and (3) received the shock dose of egg white intravenously.

We shall now consider some experiments in which the animals were allergized by the parenteral route, but in which either the protective food digest or the subsequent shock-dose of egg white was administered orally.

Experiment 6 shows what happened when treatment consisted in administering the food digest by mouth on three consecutive days—in contrast to the results shown in Example 1, where the digest was administered intravenously at ten-minute intervals. The reasons for setting an interval of some sixty-six hours between the first oral administration of the digest and the administration of the shock dose of native protein, and for giving the shock dose shortly after the digest on three consecutive days, will be discussed in some detail in our third<sup>12</sup> communication, which will deal exclusively with the immunologic conditions of orally administered propeptans. Here we merely shall state that propeptans, given orally, afford protection five times against minimal lethal doses and more. However, also this treatment brings about only partial neutralization of the antibodies,

as shown by the positive, although definitely weaker, reactions following the Schultz-Dale test and the lung perfusion test (Figs. 8 and 9).



Fig. 9. Lung perfusion test performed upon the lung of a guinea pig No. 807 allergized to egg white treated orally with egg digest followed by intravenous injection of multiple shock doses of egg white (three treatments). The animal was killed *six hours* after the last shock dose. The lung (*left*) showed an attenuated reaction to egg white, indicating partial neutralization of the antibodies. A control lung of a nonallergized animal of the same weight (*right*) showed a negative reaction in the lung perfusion test.

### Experiment 6

Guinea pig No. 807 allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline.

Three weeks later the following treatment was instituted.

*Treatment.*—(1) Oral treatment with Egg Digest (20 mgs. of Soluble Nitrogen) +0.2 grams of Glycyrrhiza +3.0 c.c. of water.

Sixty-six hours later—(2) Oral treatment with Egg Digest followed in one hour by 2.5 M.L.D. of egg white intravenously—Bristling

Twenty-four hours later—(3) Oral treatment with Egg Digest followed in one hour by (1) 2.5 M.L.D. of egg white intravenously—Bristling

(2) 5.0 M.L.D. of egg white intravenously—Bristling and gagging.

Twenty-four hours later—(4) Oral treatment with Digest followed in one hour by

(1) 2.5 M.L.D. of egg white intravenously—Bristling

(2) 5.0 M.L.D. of egg white intravenously—Bristling

Six hours after the last shock dose the animal was killed.

Schultz-Dale test—Attenuated positive (Fig. 8)

Lung perfusion test—Attenuated positive (Fig. 9)

But when the order is reversed—that is to say, when the digest is administered by intravenous injections and the shock dose of native protein is then given by mouth (Experiment 7)—the Schultz-Dale test is negative and the lung perfusion test gives an attenuated positive reaction corresponding to the conditions observed in Experiment 1.

*Experiment 7*

Guinea pig No. 757 allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white.

Three weeks later the following treatment was instituted.

*Treatment.*—Intravenous injections of Egg Digest at ten-minute intervals.

- Injection 1.—Egg Digest representing 1.0 mg of Soluble Nitrogen—No reaction
- Injection 2.—Egg Digest representing 2.5 mgs. of Soluble Nitrogen—No reaction
- Injection 3.—Egg Digest representing 5.0 mgs. of Soluble Nitrogen—No reaction
- Injection 4.—Egg Digest representing 10.0 mgs. of Soluble Nitrogen—Slight bristling
- Injection 5.—Egg Digest representing 20.0 mgs. of Soluble Nitrogen—Bristling

Thirty minutes after the last injection.

Shock-dose—By mouth 7.5 c.c. of egg white

Symptoms—Twitching of nose and gagging about ten minutes after the shock dose

Animal killed two hours after the shock dose

Schultz-Dale test—Negative

Lung perfusion test—Attenuated positive.

On the other hand, when the food digest is replaced by equal quantities of native protein, administered on seven consecutive days and then followed by the shock dose (either intravenously or by mouth), the animals are indeed protected, but there has been no antibody-neutralization, as shown by the fact that both the Schultz-Dale test and the lung perfusion test are strongly positive (Experiment 8). This conforms perfectly with the findings in Experiment 3.

*Experiment 8*

Guinea pig No. 818 allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline. Three weeks later the following treatment was instituted.

*Treatment.*—Oral administration of egg white representing 20 mgs. of Soluble Nitrogen +0.2 grams of Glycyrrhiza, every day for seven days.

(Animal starved in empty cage overnight.)

- 1st Dose—11/ 7/44—No reaction
- 2nd Dose—11/ 8/44—No reaction
- 3rd Dose—11/ 8/44—No reaction
- 4th Dose—11/10/44—No reaction
- 5th Dose—11/11/44—No reaction
- 6th Dose—11/12/44—No reaction
- 7th Dose—11/13/44—No reaction

One hour after the seventh dose—

Oral administration of shock dose 7.5 c.c. of egg white +0.2 grams of Glycyrrhiza. No clinical symptoms noted.

Six hours later—

The animal was killed and a Schultz-Dale test and a lung perfusion test were performed.

Schultz-Dale test—Positive

Lung perfusion test—Positive

Similar results are obtained when gradually increasing doses of native protein are administered by mouth on seven consecutive days (Experiment 9). This conforms with the findings in Experiment 4.

Experiments 2, 6 and 7 on the one hand and Experiments 3, 4, 8 and 9, on the other hand, show that there is a difference between the immunologic effects of food propeptans and of native protein, since the former bring about, at least, partial and temporary de-allergization as shown by the

negative or attenuated Schultz-Dale test and the lung perfusion test. Food propeptans induce micro-shocks, and thus lead, first, to partial and temporary, and, later, to complete but temporary de-allergization. Native protein, on the other hand, leads to an increase in the number of circulating antibodies, and thus to temporary hyposensitization.

### *Experiment 9*

Guinea pig No. 819 allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline.

Three weeks later the following treatment was instituted.

*Treatment.*—Oral administration of daily increasing doses of egg white +0.2 grams of Glycyrrhiza.

1st Dose—11/ 7/44—0.25 c.c. of egg white—No reaction  
 2nd Dose—11/ 8/44—0.50 c.c. of egg white—No reaction  
 3rd Dose—11/ 9/44—0.75 c.c. of egg white—No reaction  
 4th Dose—11/10/44—1.0 c.c. of egg white—No reaction  
 5th Dose—11/11/44—1.5 c.c. of egg white—No reaction  
 6th Dose—11/12/44—2.0 c.c. of egg white—No reaction  
 7th Dose—11/13/44—2.5 c.c. of egg white—No reaction

Six hours after the last dose the animal was killed.

Schultz-Dale test—Positive

Lung perfusion test—Positive

### DISCUSSION

Food propeptans (i.e. food proteins digested enough to be free of native protein, but not to the point of losing their type specificity) do not, in themselves, afford protection. It is only when they are followed by administration of the given food allergen that they bring about a more or less lasting state in de-allergization, the duration depending on the manner in which the propeptans are administered (quantity, timing, route).

When an animal has been given intravenous injections of mounting doses of propeptans, followed by intravenous administration of multiple shock-doses, and the animal is killed one hour after treatment, the Schultz-Dale test method will reveal no antibodies in the uterus, but the lung perfusion method will disclose the presence of an abundance of antibodies in the lung. However, when the animal is sacrificed six hours after the shock dose, both uterus and lungs are free of antibodies (negative Schultz-Dale and lung perfusion tests). In other words, it takes about six hours for the antibodies in these two organs to be neutralized. The reason why it takes the antibodies of the lung longer than the antibodies of the uterus to be neutralized, can, in all probability, be found in the simple fact that the lung is by far the larger of the two organs and thus contains a greater number of antibodies, and, moreover, in the fact that the lung is the primary shock organ in the guinea pig. However, while neutralization of the antibodies is complete after six hours, it is only temporary: twelve hours after the administration of the shock dose, the Schultz-Dale test and the lung perfusion test are again positive.

On the other hand, when the skeptophylactic treatment is administered by intravenous injections of gradually mounting doses of minute quantities of the native (i.e. undigested) food protein, clinical protection is also

achieved, but no neutralization of antibodies can be demonstrated (both Schultz-Dale and lung perfusion tests positive). Thus, even these minute quantities of native protein are apparently too great to elicit micro-shocks which alone are able to neutralize (sate) the antibodies. These experiments demonstrate, therefore, that from the immunologic, as well as, from the therapeutic viewpoint, the food digests (propeptans) are superior to the native proteins.

The immunologic action of the food propeptans may be explained in the following manner: they engender micro-shocks which, in turn, lead to specific skeptophylaxis (anti-anaphylaxis of Besredka<sup>1</sup>). These propeptans bring about, first, partial and transient, then complete but transient, and, ultimately, complete and lasting neutralization (satiation) of the tissue antibodies. To this immunological state the term "de-allergization" is applied by the senior author.<sup>7</sup>

#### SUMMARY

Exhaustive animal experimentation with food digests (food propeptans) show that food propeptans, given enterally or parenterally under appropriate conditions as to quantity and time, can protect guinea pigs against otherwise certain anaphylactic death.

The immunologic principles on which the protective action of food propeptans are based were studied experimentally and are discussed in some detail. As has been previously shown by the senior author there are two basic approaches by which to achieve clinical protection against anaphylaxis, namely, de-allergization and hyposensitization. Further experimental proof is presented.

Food propeptans operate by inducing micro-shocks causing first partial and temporary, later complete and lasting, satiation of the antibodies, thus, leading to de-allergization. On the other hand, native protein administered every day or every second day in the same or graduated doses increase the circulating antibodies leading only to temporary hyposensitization.

The results of these investigations seem to constitute experimental confirmation of the therapeutic value of specific propeptan therapy in food allergy in man.

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# COMBINED HELIUM AND EPINEPHRINE THERAPY

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THE use of helium and oxygen mixtures for the relief of asthma was originally suggested by Barach<sup>2</sup> in 1935. Epinephrine 1-100 by inhalation was suggested by Graeser and Rowe<sup>4</sup> in the same year. Epinephrine by inhalation had been used previously by Camps<sup>3</sup> in England but never in the very effective strength of 1-100. Both of these methods for the symptomatic relief of asthma have met with widespread acceptance and their usefulness is indeed very great.

The combination of the two in an easily utilized and if need be portable unit presents a method of quick and effective relief for most acute paroxysms of short duration and moderate intensity.

## APPARATUS

Large cylinders of oxygen and helium (size C) are used in the hospital or the office. To these are attached the usual step-down gauges which indicate the volume of gas remaining in the tank as well as the liter flow per minute. High-pressure rubber tubing carries the gas to a stand which holds the face mask, rebreathing unit and circle filter, as well as several flowmeters which measure the flow of oxygen and helium in cubic centimeters and liters per minute (Fig. 1). The epinephrine vaporizing unit is intimately attached to the face mask (Fig. 2). This has several advantages. The patient is required to do nothing but breathe deeply. There is no change necessary in the shift from helium and oxygen to the epinephrine vapor and back again if need be. The vaporizing unit used is the DeVilbiss No. 40 which in general use has been found to be very effective and which because of its large transverse diameter of outlet allows a large amount of vapor to come forth. This unit can easily be removed from the machine for cleaning and the addition or replacement of fresh mixtures of epinephrine 1-100. It can be cut off from the machine by means of a sliding diaphragm (Fig. 2). This allows the unit to be used for the helium and oxygen. It is hoped that some future design might make the use of helium and oxygen mixture and the epinephrine simultaneous. The epinephrine used is of the glycerinated variety using Lockey's formula.<sup>5</sup> As pointed out by Suszman<sup>6</sup> and by Abramson<sup>1</sup> this is the most readily vaporized and gives the finest droplet formation and hence best permeation of the bronchial tree.

There are three flow meters. One measures the amount of helium, the second the amount of oxygen to the helium-oxygen bag, and the third uses oxygen or compressed air to vaporize the epinephrine 1-100.

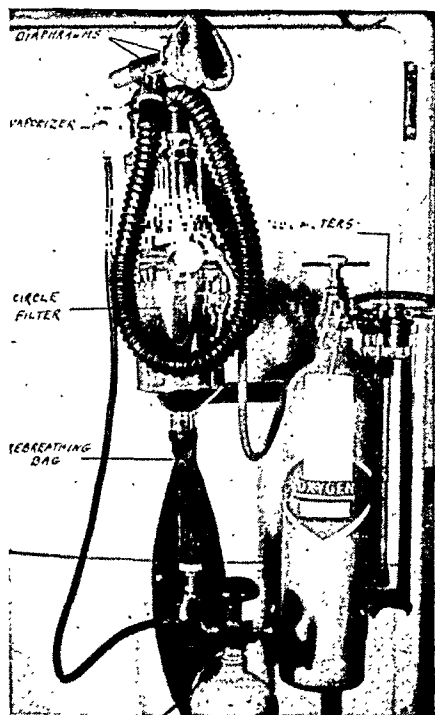


Fig. 1. Illustration of the component parts of the apparatus.

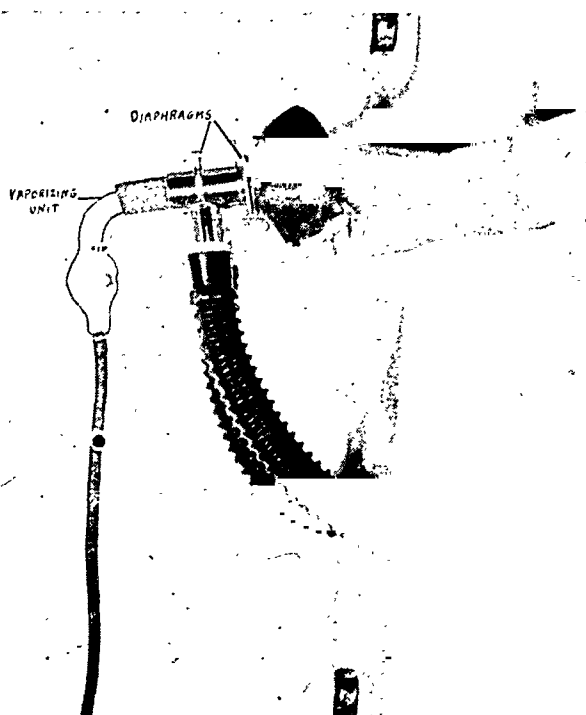


Fig. 2. Relationship of the mask to the vaporizing unit.

#### METHOD OF ADMINISTRATION

The patient is seated in a comfortable chair. If he is very apprehensive of the apparatus—and very few are, even the youngest of children have accepted it—he is allowed to hold the face mask instead of fastening it to him by elastic rubber bands (Fig. 3). A reasonable type of approximation should be made to avoid the escape of gases. The patient is then asked to breathe deeply while the epinephrine vapor is administered. Long deep inhalations are preferable to short shallow ones. After approximately thirty seconds—six to ten breaths—the vapor is discontinued and the helium-oxygen mixture administered by shifting the diaphragms on the face mask. Once the helium-oxygen mixture is established it is only necessary to add a small amount of oxygen as it is used up by the patient. This provides a definite economy, since helium is an expensive gas. The patient is allowed to breathe the mixture for about ten minutes, and frequently a return to the epinephrine vapor for three or four breaths is advisable.

More often the relaxation occurs within the first few minutes of treatment. At the termination there is often a coughing spell with variable amounts of sputum—sometimes unbelievable amounts. The pink color of the sputum is due to the oxidized medication. Occasionally the quantities of sputum are out of proportion to the physical findings of the chest and the clinical severity of the asthma. There are innu-

merable variations as to the amount of epinephrine vapor and helium and oxygen that may be inhaled. One should be guided by the clinical requirements of the case.



Fig. 3. The mask in place, showing the approximation by means of an elastic head support.

#### DISCUSSION

An inexperienced person can be trained to operate the apparatus satisfactorily. There is no danger of asphyxia with helium if oxygen is always used first in filling the bag and the helium added afterward. If one is particularly concerned with this point the 80 per cent helium-20 per cent oxygen mixture can be used instead of pure helium.

It is noteworthy that where organic obstruction is present, or where the mucous plugs are specially inspissated, the relief will be only partial, or completely absent. It is frequently desirable to administer iodides prior to treatment, particularly when the first treatment has been unsatisfactory. When no relief or slight relief is obtained, the diagnosis of allergic asthma should come under scrutiny to rule out the possibility of obstruction by neoplasm, enlarged bronchial nodes, foreign body, et cetera. In those cases, x-ray and bronchoscopy should be used.

The usual cautions and contraindications in the use of epinephrine 1-100 should be borne in mind. The use of helium and oxygen alone gives some relief for the duration of its application only, and from the standpoint of the ambulatory patient is not worth while. Helium and oxygen



for the cyanotic patient, of course, is still indicated, but such a case should be hospitalized.

Significant in the use of the apparatus is the low cost of operation. Smaller portable units, using size D cylinders, can be used, but unless portability is of prime importance, it is not desirable because of the expense.

In order to better indicate the types of cases most benefited, the following classification is suggested:

1. *Complete loss of pulmonary reserve*—dyspnea at rest.

A. Temporary—less than seventy-two hours and due to bronchospasm with or without edema and mucus which is not inspissated. These cases are greatly aided by combined therapy.

B. Those of longer than seventy-two hours—usually with inspissated mucus. These cases are not effectively relieved for anything but a very short time. However, if iodides are given in full therapeutic doses and then followed by this combined therapy, a pulmonary cleansing with very beneficial result is often effected. These cases may have to be bronchoscoped.

2. *Partial loss of pulmonary reserve*—no dyspnea at complete rest, but evoked with effort.

A. Evoked with mild effort.

B. Evoked with moderate to marked effort.

These cases are benefited in inverse proportion to the amount of bronchial mucus and edema present.

3. *No loss of pulmonary reserve*. These cases are in the interparoxysm stage and hence need only basic allergic care without any symptomatic treatment. It is understood that the above classification makes the assumption of a normal cardiac function and a lack of irreversible pulmonary pathology such as emphysema, bronchiectasis, pulmonary fibrosis, et cetera. The effect of the combined therapy can be demonstrated within fifteen to twenty minutes after the conclusion of treatment by the determination of the vital capacity.

It has been found that the use of the apparatus will relieve an acute paroxysm in the office with practically no blocking effect on skin-testing procedures.

It is noteworthy that this apparatus can be used to vaporize any vaporizable material and therefore other combinations of therapy requiring the mixture of gases and vapors can utilize this apparatus. (The use of penicillin in this apparatus is a possibility.)

#### CONCLUSIONS

1. A method of combining the use of epinephrine 1-100 and helium and oxygen in one apparatus is presented.

2. The use of expensive gases is kept down to a minimum by re-breathing, using the circle filter.

3. An effective method of speedy bronchial relaxation with minimal side effect for ambulatory patients is presented.

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## THE DIAGNOSTIC VALUE OF THE EOSINOPHILE IN ALLERGIC STATES

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HISTAMINE release and the relation of eosinophiles to the allergic reaction still remain controversial. Code<sup>1,2</sup> first used the normal rabbit to determine the relative proportion of the histamine content of the cells compared with the plasma. His findings were quite consistent in that the "white cell layer" between the plasma and red cells in the centrifuged specimen of normal whole blood contained almost "ninety per cent of the histamine content of the whole blood when compared to the plasma and red cells." Other observations by Code on the changes of the histamine content in various animals, particularly the guinea pig and the dog, during anaphylactic shock, showed that the histamine values rose three to nine times in the shocked animals, the escape of histamine taking place in the white cell layer, chiefly from the eosinophiles. Code<sup>3</sup> concluded that histamine released during the anaphylactic shock was an important factor in producing the symptoms and pathologic changes in the reaction. There is no doubt that histamine plays a very important part, whether primary or incidental, coincident with the damaged sensitized cell in anaphylaxis and allergy. Code and Macdonald<sup>4</sup> reported cases of eosinophilia in which the histamine content of the blood was above the normal. Rose<sup>14</sup> also has reported cases of eosinophilia with an increased histamine level in the blood. In other cases of eosinophilia, the blood histamine was definitely below normal. The observations of Randolph and Rackemann<sup>13</sup> showed that five of eight cases with bronchial asthma had eosinophile counts which were comparatively higher than those recorded by Code and Macdonald but the blood histamine level was normal. These observations should justify the consideration of the eosinophile response as a very important primary factor in the allergic mechanism. Clinical observations of the eosinophile in allergic states, therefore, seem justified. These observations, although elementary, are based upon our experience in studying nasal secretions and blood smears for the presence of eosinophilia.

Our observations have extended over a period of several years and comprise the evaluation of more than five thousand smears of the nasal secretions and the blood.\* This report represents an effort to stimulate the use of these valuable procedures, which Hansel<sup>6</sup> has so well established. Based upon the information thus obtained, we believe that a cytologic examination of the blood or nasal secretion ranks second to a careful history<sup>16</sup> and should precede the other diagnostic procedures, such as skin tests, et cetera. A nasal examination may be misleading and inconclusive if it is not preceded by a thorough, intelligent history with ref-

\*The major portion of this work comes from the St. Francis Hospital Allergy Clinic with the technical assistance of Miss Mary Walter.

erence to allergy, and followed by proper study of the nasal secretion. Other observers in widely separated areas have also recorded the fallacy of relying upon local nasal examination alone. In the Pittsburgh area smog, smoke and irritating chemical particles may cause a very red nasal mucous membrane in allergic patients. The following three cases corroborate the foregoing statements:

*Case 1:* D. M., aged eleven, reported to the Nose and Throat Clinic in September, 1940, on account of enlarged tonsils and for consideration of a tonsillectomy. The history of allergy was recognized; an allergic survey and control were instituted. The nasal smear showed many eosinophiles and they were also increased in the blood. She is much improved now. Tonsillectomy may be performed later if the indications justify it. It should not be instituted with the idea of controlling the allergic symptoms.

*Case 2:* W. H., aged four, reported to the Clinic with a history of "always being in the hospital" on account of "severe colds" and convulsions. After an allergic survey, including a nasal smear which revealed no eosinophiles but many organisms, bacterial vaccine was given with excellent results. This boy has been followed for four years, during which time he has had three slight respiratory infections. Recently the first convulsion, since bacterial immunization was started, was noted during an attack of scarlet fever. On the basis of these observations common cold vaccines should not be administered before the allergic state is known and the presence of many organisms is demonstrated in the nasal secretion.

*Case 3:* E. S., aged eleven, gave a history of "severe sinus trouble." Several nose and throat operations gave no relief; in fact, probably made him worse. Eosinophiles were noted in the nasal secretion. They were moderately increased in the blood. Allergic management has resulted in marked improvement. Had it been instituted earlier many operations may have been avoided. This patient has been observed for three years. He has gained 25 pounds and has been almost free of nasal symptoms until last winter. Some of his nasal symptoms returned after he ate some foods to which he was clinically sensitive.

These case reports were presented to emphasize the value of nasal smear studies in differentiating allergy from infection in children. From the symptomatic standpoint allergy may simulate acute or chronic infection.<sup>12</sup> Correct diagnosis may be established only by repeated study of the nasal secretions. Hansel<sup>8</sup> has emphasized the value of the allergic investigation before recommending nose and throat operations. During the past few years better co-operation among the pediatrician, the otolaryngologist and the allergist has developed. By this co-operation unnecessary tonsillectomies may be avoided.

Is the eosinophile related to the immunologic response? For many years it has been recognized that eosinophilia will fluctuate with immunologic reactions. It is particularly significant in nasal allergy that when the pH of the nasal secretion falls low or toward the acid side there is a complete disappearance of the eosinophiles. When the pH returns to the alkaline side there is a return of the eosinophiles. Kaufman<sup>10</sup> states that "The relationship between eosinophilia and allergic disease is not clear."

EOSINOPHILE STUDIES ON 100 CONSECUTIVE PATIENTS VISITING THE  
ALLERGY CLINIC

Number of Patients.....	100
Number of Nasal Smears.....	60
Eosinophiles only .....	7
Eosinophiles and neutrophiles.....	6
Eosinophiles and organisms.....	9
Eosinophiles, neutrophiles and organisms.....	27
	—
	49
Neutrophiles only.....	3
Organisms only .....	4
Neutrophiles and organisms.....	3
	—
	11
Number of Blood Smears.....	39
Eosinophilia over 5 per cent.....	18

Three primary sources of the eosinophile have been considered: (1) the local shock tissue, (2) the blood, and (3) the bone marrow or other blood-cell forming organs.

Some observers believe that eosinophiles may be formed in the local tissues. Salaris and Guarnari<sup>15</sup> reported the following ingenious experiment:

Fifteen patients suffering from bronchial asthma or allergic rhinitis were tested intracutaneously with specific allergens. Blood was drawn from the finger tip at five, twenty, forty and sixty minutes, respectively, after the onset of the positive cutaneous reaction and the percentage of eosinophiles was determined. An increase in eosinophiles was noted within five to twenty minutes. This increase was more pronounced in the blood taken from the arm on which the cutaneous testing was performed. This finding according to the authors is suggestive of the local origin of eosinophiles. Their findings could not be duplicated in an extremely sensitive individual.

Patient C. R., aged twenty-two, was admitted to the hospital, December, 1942, in severe shock, unconscious, and with compound fractures of both legs. No tetanus antitoxin was given because the history suggested a severe sensitivity to horse serum. The allergic symptoms were asthma, urticaria, rhinitis and gastro-intestinal upsets to certain foods. An allergic survey was done several weeks later during the convalescence.

*Intradermal Skin Tests*

Positive tests were obtained to many foods and inhalants.

Dust (1-10) +++

Mustard ++++

Grass (1,000 PNU/cc) +++

Peanut ++++

Tests for mustard and peanut were performed at one sitting. A constitutional reaction resulted.

*Horse Serum*  
 1-1,000,000 +  
 1-100,000 +++  
 1-1000 ++++

*Horse Dander*  
 1-4,000,000 0  
 1-400,000 +++  
 1-40,000 ++++

At the time of a skin test to horse dander, 1-40,000 dilution the blood showed three per cent eosinophilia. Fourteen minutes later there was a two per cent eosinophilia and the horse dander reaction was four plus.

Occasionally it is necessary to study the eosinophile content of other tissues or body secretions, depending upon the nature and location of the allergy. Eosinophiles may occur in large numbers in the stools of patients suffering from gastro-intestinal allergy, in the urine in urinary system allergy, in sections of nasal polyps or in the appendix and other pathologic tissues. Antral washings may be quite revealing. Operations on the nose of patients with nasal allergy may be instrumental in aggravating the allergic symptoms. Dutton<sup>5</sup> suggests that frequently allergic reactions precede the infection of appendicitis just as there are seen infections super-imposed on allergic asthma. He based his conclusions upon a detailed study of the eosinophiles noted in the pathologic sections from one hundred and twenty-three appendices removed in cases of appendicitis.

An increased eosinophilia may occur in other disease processes such as in parasitic infestations; consequently, one should be cautious in considering an eosinophilia to be allergic in origin in the presence of any other disease associated with this phenomenon. Pulmonary eosinophilic infiltration or "Loeffler's syndrome" is considered by many as an allergic reaction. Communications from military observers from many parts of the world point out that eosinophilia is noted in many diseases occurring in the tropics other than those suspected previously. Some of these observers believe that occasionally the eosinophilia is similar to that found in "Loeffler's syndrome." Familial eosinophilia has also been reported on several occasions. Our observations would indicate that the presence of five per cent eosinophiles in the blood, or above, is an increase. In our patients the eosinophilia varied from five to twenty per cent and on rare occasions it was increased to as high as 35 per cent. An eosinophilia without a demonstrable allergic cause was not observed more than three to four times.

#### METHODS OF OBTAINING NASAL SMEARS

1. Have the patient blow his nose upon wax paper or cleansing tissue.
2. Swab-stimulation is used when the nasal mucosa is fairly dry. This method has not been very satisfactory. It is time-consuming and as a rule only watery secretion and epithelial cells are obtained.
3. The material may be obtained by having the patient "hawk" in instances in which a post-nasal discharge is present.

The first method is preferred as a majority of patients usually have considerable nasal discharge. If secretion is not available at the time of

the examination, the patient is given a packet consisting of two clean slides, toothpicks and waxed paper. He is instructed to make two slides at different times and to bring them to the Clinic or office at the next visit. If the patient is well instructed this method is very successful.

When changes occur in the symptomatology a smear should be examined. It is often necessary to determine whether or not a common cold is present. Hansel<sup>7</sup> emphasizes the importance of following these changing conditions by repeated examination. Occasionally it may be noted that there is a difference in the cytologic picture in specimens taken from each side of the nose.

#### PREPARATION OF THE SLIDES AND STAINING

Giemsa, Wright's Eosin-methylene blue, or Hansel's stain may be used. Recently Hansel has supplied us with his latest polychrome stain. The staining is accomplished with one solution. It stains bacteria also. This new stain has given excellent results. The value of cytological studies of nasal secretions cannot be overemphasized to the student. He should be taught that nasal smear examination is as simple as differential blood counting and frequently almost as important.

The simple staining method using Wright's is as follows:

The secretion is spread thin on the slide and allowed to dry in clean air. After it is completely dried, the Wright's stain is applied and then the distilled water. Wash with distilled water. As a general rule the staining times are one-half that for blood smears. Stand the slide on end or dry over a small electric bulb. Do not blot.

Hansel's<sup>9</sup> technique for nasal and bronchial secretions with his new stain is as follows:

1. Collect secretion by having patient blow nose on waxed paper.
2. Transfer secretion to slide—tease out with toothpick so as to avoid thick masses. Make two or three smears if there is enough material.
3. Dry smears in air or gently over a flame.
4. Mark across slide next to label with paraffin stick to prevent overflow.
5. Cover completely with stain and allow to stand thirty to forty-five seconds, giving the longer period to thick or sticky smears.
6. Add distilled water to take up stain as in Wright's technique and allow to stand about thirty seconds. For best results neutralize the distilled water by adding one drop of one per cent potassium carbonate to each 30 c.c.
7. Pour off stain and flood slide with distilled water to remove excess stain.
8. Flood slide with 95 per cent ethyl alcohol. Drain off and dry slide over a flame.
9. If the blue color is too intense, flood slide with ninety-five per cent

ethyl alcohol to which one drop of one per cent hydrochloric acid has been added to 30 c.c. The amount of blue color removed depends upon the length of time the acid-alcohol is allowed to remain on the slide.

10. Pour off acid-alcohol and then flood with plain 95 per cent ethyl alcohol again.

11. Always examine the stained smear under the microscope before using the acid-alcohol solution. The acid treatment intensifies the red in the eosinophile by removing overlying blue. Too much acid may take the blue out of the neutrophiles and give them a pink color. If the neutrophiles are pink upon the first examination, stain another specimen and allow about fifteen to twenty seconds longer for the stain to act before adding the water.

12. In the examination of smears, the magnification must be 125 to 150. Using a 10 x objective, the eye piece, therefore, should be 12.5 or 15 x. Use a moderately strong clear light.

All the slides should also be examined with the oil emersion lens; this is essential to bring out the cellular details and to recognize bacteria. It greatly limits the size of the field, however, and more time is required for examination. A cover slip should not be used.

The characteristics of the eosinophile are as follows:

1. It is larger than the neutrophile.
2. The cellular membrane is fragile and many broken cells with loosely scattered eosinophilic granules may be observed.
3. The nuclei are usually two in number and stain blue.
4. The cytoplasm is filled with large acidophilic granules which stain brilliantly orange-red.

No cell should be designated as an eosinophile unless it conforms to this description.

Although preliminary experiments have been inconclusive, some observers have presented sufficient evidence to suggest that the production of eosinophiles is in some manner related to the release of histamine. Code<sup>1</sup> has shown that the principal source of histamine in the blood stream is probably the circulating eosinophiles. To explore this premise a patient with exfoliative dermatitis was given intravenously the salt equivalent of one mgm. of histamine. At the time of the injection the eosinophile count was three per cent and twelve hours later it was 5 per cent. This was not a significant rise. A higher count might have been incurred earlier. Moon, Lieber and Kennedy<sup>11</sup> showed that in normal individuals after the intravenous histamine, leukocytosis took place in three to five hours.

The cytoplasm<sup>4</sup> of the polymorphonuclear cells of the dog is almost devoid of stained material and relatively few eosinophiles are present. In contrast to this the polymorphonuclear cells of rabbit blood contain eosino-

phile granules. This is the normal appearance of rabbit blood and the cells have been referred to by hematologists as pseudo-eosinophiles. These observations in animals might suggest that reversible chemical compounds in the cytoplasm of the polymorphonuclear cell determine the size and staining qualities of the granules.

#### INTERPRETATION

The clinical observer should evaluate the significance of the smears at the time of the examination of the patient. An allergy laboratory in the clinic to facilitate handling of the slides is a distinct advantage.

In the cytologic examination all the elements in the smear should be observed and recorded. The organisms can easily be identified for they stain blue or purplish with the stains mentioned previously. The type of organism can often be identified. When the slide shows many organisms, a bacteriologic study of the secretion is indicated.

The eosinophiles may be very unevenly distributed or they may be conglomerated in a clump of mucus. One clump in the entire specimen may show hundreds of eosinophiles. An occasional eosinophile, especially in children, may be regarded as normal. A few neutrophils are normally observed.

The presence of epithelial cells does not signify anything pathological. In a case of a sarcoma of the maxillary antrum, however, many sarcomatous cells were noted in the nasal smear. The diagnosis could have been made without the smear but it furnished substantiating proof.

#### MAJOR TYPES OF RESPONSES

##### 1. *Allergy*

E + + + +	N 0	Or 0	Ep + —
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##### 2. *Infections*

E 0	N + + +	Or + + +	Ep +
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##### 3. *Bacterial Allergy or a Secondary Infection on Top of An Allergic Response*

E + +	N + + +	Or + + +	Ep +
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E—Eosinophiles

Or—Organisms

N—Neutrophils

Ep—Epithelial Cells

These three general classifications should be employed in the diagnosis of rhinitis and sinusitis.

Vasomotor rhinitis of the endocrine-sympathetic nervous system type usually has a profuse watery secretion with almost no cellular content.

The secretion in cerebrospinal rhinorrhea has the characteristics of spinal fluid.

Although eosinophiles may be present in large numbers in the nasal secretion, with the development of an acute coryza, they rapidly disappear.

The following case illustrates this point:

The patient, M. C., aged 28 years, was seen at the Clinic, December 19, 1940. She stated that "hives" appeared one-half hour after breakfast Wednesday, December



19, 1940. They had extended over the entire body but were relieved by an injection of epinephrine. She thought a "cold" was developing for a period of two to three days. Her nose was running and she was sneezing. A thyroidectomy had been performed on her several years ago but the last basal metabolic rate was minus ten. Her menstrual periods were regular and the last one was finished four days ago. There was no allergic history. Food taken the day before consisted of:

eggs*	coffee*	sugar	salmon	vanilla	cheese*
wheat*	milk*	apple*	chocolate	molasses	potato

\*denotes the foods that were taken in large quantities but these were negative on intradermal testing.

December 29, 1940—The urticaria continued. The basal metabolic rate was minus eight and the temperature 98.6° F.

December 21, 1940—A nasal smear showed:

E +++++ N + — Or 0 Ep 0

Late in the afternoon of December 21, the nasal secretion increased and the next day the patient had a definite respiratory infection. Coincidentally, the urticaria disappeared.

December 25, 1940—A nasal smear showed:

E 0 N+ Or +++++ Ep +

Hansel states:

"In evaluating the number of neutrophils in the secretion one must take into consideration that the neutrophilic response is always greater than the eosinophilic response and that the number of neutrophils usually out-numbers the eosinophiles about ten to one, therefore, a plus-minus or a plus one of neutrophils represents about ten times as many eosinophiles. In a smear with four plus neutrophils the field is completely covered with them."

#### CONCLUSIONS

1. With a presentation of case histories, clinical and laboratory observations, the diagnostic value of the eosinophile in allergic states has again been emphasized.

2. A more general diagnostic use of this procedure should be employed. Besides the eosinophilia in the nasal secretions and in the blood, other more obscure symptoms may be established as of allergic origin by the recognition of this cell in the tissues involved.

3. Simple methods of collecting, staining and studying nasal smears have been presented.

4. All the elements in the nasal smear should be observed and recorded.

5. The controversial relationships between histamine release and eosinophilia have been discussed. Valuable information may be obtained by further observations on these phenomena.

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*A Study of Oils Used for Intra-Muscular Injections*. Brown, Willis E., Wilder, Violet M., Schwarts, Pauline: *J. Lab. & Clin. Med.*, 29:259, 1944.

The ideal oil for intramuscular use should meet chemical requirements of stability and neutrality; it should be inert and nonirritating biologically; and physically it should be a good solvent or dispersing medium. Four oils (corn, cottonseed, sesame and peanut) were studied by the authors. Antigenic properties were studied by injecting patients at weekly intervals with two injections of each oil. These patients were tested two months later by patch and intracutaneous tests. Reactions were uncommon, but sesame and corn oil were considered less antigenic than the other two.

Biological reactions were tested on rats and rabbits. Within 24 hours there was an increase in round cells locally and the oil was diffused through the muscles. In two to three days sections were made and the oil was found to have accumulated in small droplets surrounded by a layer of fibrin. Peripheral to this layer were leukocytes and wandering cells.

Corn and sesame oil produced the least reaction as judged by the degree of fibrin and cell infiltration. Peanut oil produced the most marked reaction.

*The Use of Histaminase in Prophylactic Tetanus Antitoxin Reaction*. Eger, S. A., and Stone, J. E.: *Penn. M. J.*, 47:371, 1944.

The authors studied a total number of thirty-one cases that developed serum reactions following the prophylactic administration of 1,500 units ATS. Fifteen of these were treated exclusively by the oral administration of twenty units of histaminase every three hours until symptom free. The untreated sixteen cases served as a control. The average period of recovery was apparently the same in both treated and control cases and there was no diminution of the intensity of symptoms in the histaminase-treated group.

## HISTAMINIC CEPHALALGIA WITH DUODENAL ULCER

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**E**VEN though histamine was first isolated from ergot almost thirty-five years ago by Bayer and Dale, it has been only comparatively recently that effective clinical applications of the drug have been reported. Histamine, widely distributed in plant and animal tissues, is probably the most powerful dilator of capillaries known. It acts on nearly every organ of the body and alters the permeability of vessel walls allowing the escape of plasma proteins into extra-cellular fluid spaces. So far, the clinical uses of histamine have not yet measured up to its probable potential and ultimate usefulness.

The use of histamine in determining gastric secretory function has been well established and it has been reported to be of value in the treatment of physical allergy, urticaria, Ménière's Disease, histaminic cephalalgia, and multiple sclerosis. In a twelve-month period fifty cases of headache were studied by one of us (R.I.A.) of which four were typical of histaminic cephalalgia as first described by Dr. Bayard Horton. One case of histaminic cephalalgia presented an unusual complicating feature and we felt this case should be reported in order to add confirmatory evidence to Horton's previous studies.

This patient is a thirty-one-year-old man, with a previous history of typhoid fever, whooping cough, mumps, and measles. He had otherwise always been in good health, with no operations or injuries. The family history is irrelevant with no record of stomach trouble or allergy.

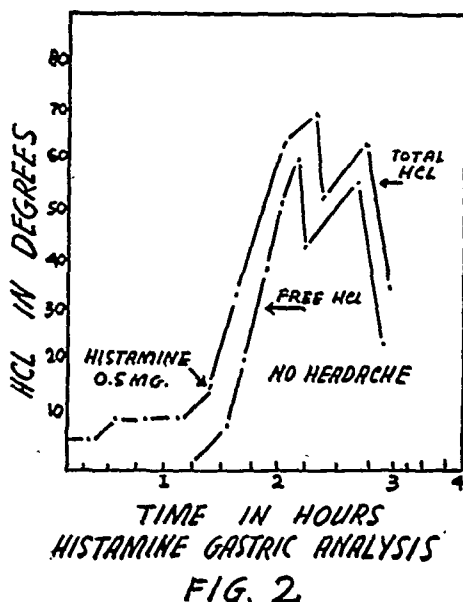
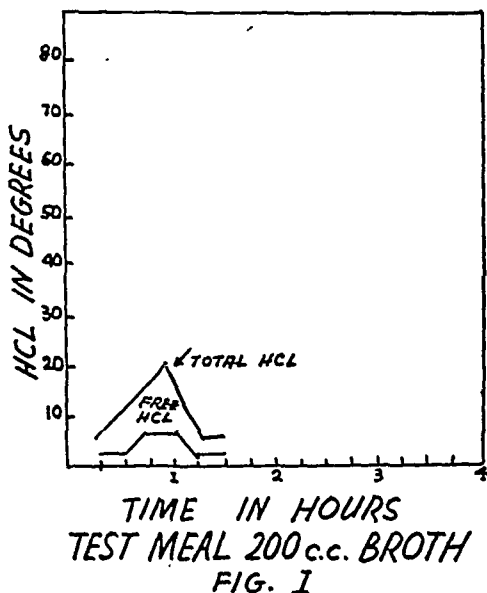
About fifteen years ago, he first noticed sharp, needlelike pain, localized to the region of the right eye. This pain lasted about an hour and came at any time of the day or night. The right eye watered, became markedly injected and the right nostril became obstructed. The pain was so severe that he was unable to remain quiet and he felt like striking his head against the wall. During this fifteen-year period he had had free intervals as long as three months, and then again he suffered from as many as three headaches in twenty-four hours. He had been treated for sinusitis.

About twelve years ago, which was three years after the onset of headaches, he noticed attacks of gnawing pain in the epigastrium for the first time. The pain came on one and a half to two hours after eating and often during the night. He vomited occasionally with relief from pain. On a number of occasions he vomited coffee-ground material and several times had vomited a cup or more of bright red blood. Tarry stools had been observed on a few occasions. The epigastric pain was relieved by soda and food. Hospitalization on an ulcer diet usually brought relief of gastro-intestinal symptoms in about two weeks. The digestive symptoms had tended to become progressively more severe and the last attack of ulcer distress continued for about five months.

Gastroscopic examination was normal. Proctoscopic examination was normal. The urinalysis and blood counts were within normal limits. The Kahn test was negative. No parasites, ova, typhoid or dysentery bacilli were found in the stools.

From the Gardiner General Hospital, Chicago, Illinois.

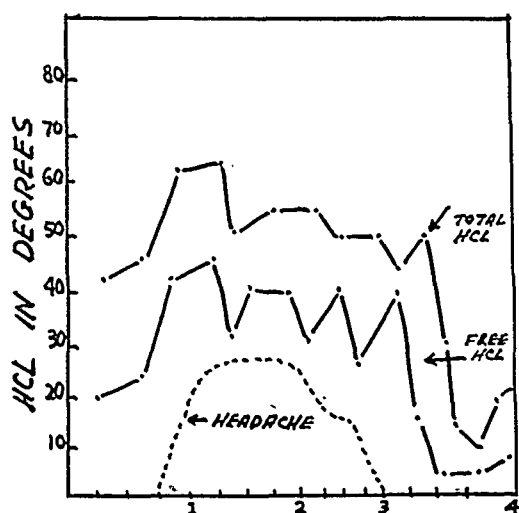
Roentgenoscopic and roentgenographic examination showed a normal esophagus and stomach. There was a marked deformity of the duodenal cap, just beyond the pylorus, and a shadow suggestive of a small crater was seen in this area. The above findings were well shown in the roentgenograms. These findings were reported as compatible with those of an ulcer of the first portion of the duodenum.



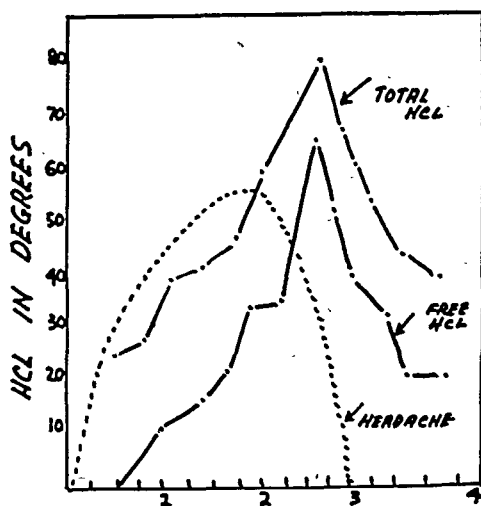
Horton reported ten cases of histaminic cephalalgia complicated by acute duodenal ulcers with demonstrable crater formation. It was demonstrated in these cases that there was a rise in gastric acidity at the time of the headache, comparable to the rise in gastric acidity produced by an injection of histamine. It was presumed that these cases presented duodenal ulcers related to the rise in gastric acidity occurring during the attacks of histaminic cephalalgia. With these observations in mind, a study was made of the relationship between histaminic cephalalgia and the duodenal ulcer in our case. The histaminic cephalalgia in our case began approximately three years prior to the development of the symptoms suggesting peptic ulcer. Furthermore, it was noted that the attacks of ulcer distress were intermittent in occurrence and coincided with the attack of histaminic cephalalgia. A study of gastric acidity following a test meal of broth revealed very low values for total and free hydrochloric acid (Fig. 1) which is an unusual finding in active peptic ulcer patients.

Histamine phosphate in a dose of 0.5 mg. used as a stimulant of gastric secretion showed a good response (Fig. 2) without production of headache. Curves of the values of total and free hydrochloric acid during typical attacks of spontaneous histaminic cephalalgia were obtained on numerous occasions. It will be noted that on one occasion while attempting to establish a base line for gastric acidity, a spontaneous attack of hista-

minic cephalalgia occurred (Fig. 3). There was a rise in free and total hydrochloric acid, that paralleled the onset, severity and cessation of the histaminic cephalalgia. Another gastric analysis curve is shown with the severity of the headache plotted simultaneously (Fig. 4). The gastric



TIME IN HOURS  
SPONTANEOUS ATTACK OF  
HISTAMINIC CEPHALALGIA  
DURING SIMPLE ACID CURVE WITHOUT  
GASTRIC STIMULANT  
FIG. 3



TIMES IN HOURS  
HISTAMINIC CEPHALALGIA ATTACK  
WITH SIMULTANEOUS  
LEVEL OF GASTRIC ACIDITY  
FIG. 4

acidity was determined following treatment with histamine and cessation of the attacks of histaminic cephalalgia. This was done following injection of 0.5 mg. of histamine and also following the use of a broth test meal. There were no significant variations between these values and those prior to the use of histamine therapeutically. Histamine consistently produced typical attacks of histaminic cephalalgia prior to use of the drug therapeutically, but produced no headache after treatment.

Although one case is statistically insignificant, these observations indicate that there is more than a casual relationship between histaminic cephalalgia and coincidental duodenal ulcer. Both the history given by the patient and the values for gastric acidity during attacks of cephalalgia are, we feel, confirmatory of this relationship between the two conditions.

It has also been shown by Hay, Varco, Code, and Wangenstein, as well as by other observers, that chronic histamine stimulation will cause peptic ulceration in experimental animals. It is theoretically possible that there is a release of histamine at the time of the occurrence of histaminic cephalalgia, causing a rise of gastric acidity that is instrumental in causing or predisposing to peptic ulceration.

McHardy and Browne reported two cases of Ménière's syndrome treated with histamine that developed duodenal ulcers, apparently as a

result of the chronic stimulation of gastric acidity by histamine. They felt that there was insufficient evidence to justify the use of histamine in the therapy of histaminic cephalalgia with concomitant duodenal ulcer.

All of Horton's cases responded to histamine treatment in so far as the histaminic cephalalgia was concerned, and the peptic ulcers were not slowed but perhaps were accelerated in their symptomatic and roentgenographic healing. This was true also in our case, as there was no apparent adverse effect on the duodenal ulcer during a prolonged series of histamine injections. Prior to and during the treatment with histamine, ulcer therapy was instituted, using frequent milk and cream feedings, a bland low roughage diet, aluminum hydroxide jel, and rest. This resulted in a prompt cessation of symptoms which did not recur following the treatment with histamine. This might be considered an objection to the significance of our results, but it is felt that ours was a patient who would never have had an ulcer if it had not been for the stimulation of the gastric acidity by the histaminic cephalalgia. The ulcer type of therapy utilized served to prevent excessive rise in gastric acidity during therapy with histamine. With ordinary care and treatment of the histaminic cephalalgia it was felt that there would be no recurrence of the ulcer. A point of interest was the effect of histamine "desensitization" on the response of gastric acidity to histamine. In our case there was no apparent change in the response of the gastric secretory apparatus. It would be of interest to follow more such cases to determine if there is a desensitization, at least as far as we can measure by gastric secretory studies.

#### SUMMARY

1. A case of histaminic cephalalgia with duodenal ulcer is reported.
2. During several attacks of headache the acid curve was high, similar to a curve resulting from the injection of histamine.
3. During periods free from headache, the acid curve showed a low acidity.
4. Following treatment with histamine the headache and the ulcer crater both disappeared with no change in the essential gastric secretory mechanism.

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# ASTHMA WITH BRONCHIAL INFECTION TREATED BY PENICILLIN

## Preliminary Report

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POOR results are commonplace in the treatment of intrinsic asthma. The outstanding successes produced by penicillin in a variety of serious infections naturally have directed attention to the use of this drug in otherwise refractory cases of asthma with bronchial infection. A recent report of the Council on Pharmacy and Chemistry of the American Medical Association reveals that penicillin is effective in staphylococcic, clostridial, hemolytic streptococcic, anaërobic streptococcic, pneumococcic, meningococcic and gonococcic infections. Its efficacy in infections due to Gram-negative bacilli, including Friedländer's bacillus, has not been established. Just as in cases of pneumonia where anatomic diagnoses are being replaced by etiologic diagnoses, the logical treatment of the bronchial infection with asthma is based on identification of the offending organism. In the first case to be presented the predominating organisms found in the sputum were alpha hemolytic streptococci and Friedländer's bacilli.

### REPORT OF CASES

*Case 1.*—Mrs. W. R., a white woman, aged fifty-six years, came to the clinic June 19, 1944, because of hemoptysis, loss of weight and symptoms of chronic bronchial asthma. She had had pansinusitis and bronchial asthma for nineteen years. During the past year she had been having a low grade fever, and since December, 1943, her condition had become progressively worse with a loss of 30 or 40 pounds in weight. During the past year she had had two attacks of hemoptysis. A Caldwell-Luc operation had been performed some years before. On physical examination the patient was found to be quite emaciated but not acutely ill. There were many whistling râles in both pulmonary fields and numerous sonorous râles, especially in the right pulmonary base. Examination of the heart yielded clinically negative findings. A roentgenogram of the chest made on the day of admission showed that the mediastinal structures were distorted by a right dorsolumbar scoliosis but were apparently within normal limits for a person of the patient's age. The hilus shadows revealed no abnormality. The lungs were extremely emphysematous. Areas of infiltration were present throughout the lower four-fifths of the right lung and the middle third of the left lung. The roentgenologist considered that this region was composed of the innumerable closely approximated punctate foci, some of which were so sharply defined and dense as to suggest that they might contain calcium. Confluence of these minute regions resulted in the formation of increased density which uniformly involved the affected portion of the lung. The diaphragm was low and the costophrenic angles blunted. There was, however, no fluid in the base of the pleural cavity. Noted, incidentally, were healing fractures of the lower left ribs in the midaxillary line.

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A culture of the sputum on June 19, 1944, revealed the presence of alpha hemolytic streptococci and Friedländer's bacilli. The Wassermann and Hinton tests gave negative results. Routine hematologic studies showed 15.1 grams of hemoglobin, 4,100,000 red blood cells, 8,500 white blood cells with 63 per cent neutrophils, 9 per cent eosinophiles and 28 per cent lymphocytes. On urinalysis a trace of albumin was found, the remainder of the urinary components being within normal limits. Studies of the blood chemistry showed 29 mg. of nonprotein nitrogen and 87 mg. of dextrose per 100 c.c. Allergic studies confirmed the impression that the patient was suffering from asthma associated with bronchial infection.

The patient had previously had two full courses of treatment with sulfonamides but with little effect. On June 26 the administration of penicillin was started; 20,000 units were given intramuscularly every four hours. After two days, dosage was reduced to 10,000 units every four hours and continued for four days, a total of 480,000 units having been given. This was not considered to be the optimum quantity needed; it was, however, all that was available. A second roentgenogram revealed findings identical with the first. A second sputum culture showed that the predominating organisms were now *Neisseria catarrhalis* and *Micrococcus tetragenus*.

*Comment:*—The patient showed definite clinical improvement following treatment with penicillin but there was little reversal of the roentgenologic findings. The dyspnea and asthma were ameliorated and the temperature returned to normal. The patient's appetite was also greatly improved. It must be stated, however, that a definite improvement in the patient's outlook preceded the administration of the drug during the first week of hospitalization for study. The amount of sputum brought up was not significantly lessened. The improvement would perhaps have been greater if larger doses of penicillin had been employed but this is doubtful because the predominating flora were completely changed by the treatment. On the basis of this case one must conclude that although penicillin will no doubt be a helpful adjunct in the treatment of asthma due to bronchial infection, it still does not affect the irreversible changes which are characteristic of long standing intrinsic asthma.

*Case 2.*—Mrs. A. S., a white woman, aged thirty-four years, presented herself August 3, 1944, because of bronchial asthma of two years' duration. Allergic studies showed her to be sensitive to ragweed and house dust. Roentgenogram of the sinuses showed polypoid degeneration of the mucous membranes of the maxillary sinuses. Sinusotomy was performed on August 5 and desensitization begun. The asthma did not improve and by August 21 she had become very much worse. Her temperature rose to 102° F. and continued at approximately this level with diurnal variations of approximately one degree. She was admitted to the hospital on August 23. Physical examination at that time revealed a well developed and well nourished white woman in status asthmaticus. She was coughing up large quantities of thick, greenish-yellow sputum, culture of which showed a predominance of staphylococci and *Str. Hemolyticus* (B.). A roentgenogram of the chest showed three areas of pneumonitis; one in the left upper lobe and one each in the right upper and right lower lobes. The largest of these measured about 5 cm. in diameter and the smallest about 1.5 cm. Routine hematologic studies showed 14,250 white blood cells with 83 per cent neutrophils, 6 per cent eosinophiles and 11 per cent lymphocytes. Blood chemistry and urinalysis revealed no abnormal findings.



On August 26 she was given 500,000 units of penicillin; this was administered intramuscularly in doses of 20,000 units every four hours. A second roentgenogram made August 31 showed that the two smaller areas of increased density had almost disappeared and the largest one had greatly reduced in size. The character of the sputum was strikingly changed in that the cellularity was considerably reduced; the sputum coughed up following administration of penicillin was clear and translucent though somewhat jellylike in consistency. As in Case 1, the second culture showed predominant organisms to be *Neisseria catarrhalis* and *Micrococcus tetragenus*. During the hospital stay the asthma improved and finally, on September 2, occasional sibilant râles only could be heard.

*Comment.*—In this second case the patient not only showed definite clinical improvement following treatment with penicillin, but there was in addition clearing of much of the pneumonitis. Again, in this second case the general outlook of the patient was much improved; a certain amount of this may be referable to the use of a dramatic drug. In contrast to the first case where changes in the lungs were irreversible, the second patient was more fortunate in this regard. Asthma, like tuberculosis, must be treated early.

#### SUMMARY

Two patients with asthma with bronchial infection were treated by the administration of 500,000 units of penicillin each. Both definitely improved, though in the first case irreversible changes in the lungs were unaffected. Penicillin has proved to be a helpful adjunct in the treatment of this type of asthma.

### Combined Helium and Epinephrine Therapy

(Continued from Page 190)

4. Portability if desired is possible, and the machine can be operated by attendants with basic instruction.
5. This apparatus can be used for other types of combined inhalation therapy.

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# URTICARIA FOLLOWING THE USE OF PROTAMINE ZINC INSULIN

## Report of Case

R. F. HUGHES, M.D., F.A.C.A. and H. R. McALISTER, M.B. (Tor.)

Hamilton, Ontario, Canada

Mrs. M. J., aged sixty, has been a diabetic since 1926, at which time she went into diabetic coma. She was discharged from hospital taking regular insulin, 20 units three times a day. She had little or no medical supervision. In June, 1944, when she first consulted us, it was suggested that she be re-balanced, and protamine insulin, requiring only a single daily injection, be used. In ten days this was accomplished, and she left the hospital taking protamine zinc insulin 30 units, and zinc insulin crystalline ten units. In another two weeks it was possible to omit the crystalline insulin entirely.

About a month after the change to protamine zinc insulin, urticaria appeared, first on the feet and ankles, later on the whole body. This urticaria was continually present, was very irritating, and did not yield to local applications.

In order to determine the cause of the condition, samples of various types of insulin were obtained from the Connaught Laboratories, Toronto, through the courtesy of Dr. R. G. Romans. We were informed that the protamine zinc insulin regularly supplied by the Connaught Laboratories is made from a mixture of insulin from beef and pork pancreas. A vial of protamine zinc insulin prepared to contain only insulin from pork pancreas was also supplied. This enabled us to perform the intradermal tests shown in Table I.

TABLE I

	Direct Test	Passive Transfer	
		Sensitized site	Control
1. Protamine zinc insulin Beef and Pork (dilution 1:10)	+	+	—
2. Protamine zinc insulin (Pork) (dilution 1:10)	++	++	—
3. Regular zinc insulin (dilution 1:10)	±	—	—

These tests indicate that the patient was sensitive on both direct and passive transfer tests, to both types of insulin containing protamine, but not to insulin in which protamine is not present. One would conclude from this that protamine (salmine) was the cause of the urticaria. Unfortunately, it was not possible to obtain a sterile specimen of salmine for testing.

Treatment in this case presented difficulties, as the patient was obliged to return to her home in the United States, in order to validate her passport. In addition, it was necessary to continue to use insulin as prescribed. Under these restrictions, an attempt was made to carry out skeptophylactic deallergization, by having her take  $\frac{1}{2}$  unit of regular insulin and of protamine zinc insulin forty-five minutes before her prescribed doses. This was intended to bring about a refractory period, during which the full dose might be given without bringing about the urticarial reaction. However, this was not successful, and was abandoned

after three days trial. A second skeptophylactic method was then tried.<sup>4</sup> This consisted of the administration of protamine zinc insulin in doses of 1, 2, 3, 4, 5, 6, 7, and 8 units (total 36 units) taken at fifteen-minute intervals, followed by 15 units regular insulin, and breakfast. After four days' trial, without result, this was also abandoned, and the conventional treatment was restored.

As a final effort, histamine azo-protein\* was given by hypodermic injection in doses of 0.1, 0.15, 0.2 et cetera at three-day intervals, and a prompt and gratifying relief of symptoms was the result. A report was obtained from the patient four weeks later, which indicated that there had been no return of urticaria since the latter treatment had been instituted.

#### DISCUSSION

Since the introduction in 1936 of protamine zinc insulin, reactions of various types following its use have been reported. These have included local reactions, generalized urticaria and angioneurotic edema. Kern<sup>3</sup> reported a case of purpura following the use of both regular and protamine insulin. Bronchial asthma together with generalized urticaria and angioneurotic edema was observed by Herold<sup>1</sup>, in an asthmatic patient under protamine zinc insulin treatment for diabetes.

Local allergic manifestations are very common with protamine zinc insulin. Probably well over 50 per cent of patients complain of an itching or burning sensation at the site of injection, and on the day following an area of erythema is visible, which usually disappears in another twenty-four hours. Invariably these patients require no specific treatment, and within two to three weeks the local reactions entirely disappear. In a comprehensive review of insulin allergy<sup>2</sup> on the basis of animal experiments and clinical observation, it is stated that the protamine fraction may be excluded as an etiological factor in cases of allergy to protamine zinc insulin. However, this case appears to illustrate an unusually prolonged urticarial reaction which was apparently due to the protamine fraction of the insulin in use. This is not unexpected, since many cases of hypersensitivity occur following the use of similar protein or protein components. Schick, in his lecture† to the Fourth Annual Forum of Allergy, stated that it was his opinion that the most common and potent allergens are of embryonic nature (eggs, seeds, nuts, pollen grains, fungus spores). Protamine (salmine), being derived from the sperm of the salmon, is of this nature, and hence it is not surprising that an allergic reaction should occur after parenteral injection of insulin containing this substance.

#### SUMMARY

1. A case is presented showing an allergic reaction (urticaria) following the use of protamine zinc insulin.
2. Skin tests direct and passive transfer, indicate that the allergen was present in the protamine zinc insulin but not in regular insulin.

\*Hapamine, Parke Davis & Co.

†Unpublished.

3. Treatment by specific (skeptophylactic) method was unsuccessful.
4. Relief was obtained with a histamine conjugate (Hapamine, Parke, Davis & Co.).
5. The incidence of protamine zinc reactions is discussed.

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*Effect of Beta-Hypophamine and Suprarenal Cortex Extracts on the Prevention of Histamine Shock in the Guinea Pig.* Wittich, F. W.: Ann. Allergy, 1:154, 1943.

Guinea pigs of uniform stock and weight were used to determine the lethal dose of histamine and the effect of previous injections of suprarenal cortical extract (Eschatin, each c.c. containing 25 dog units) and Beta-Hypophamine (Pitressin, each c.c. containing 10 pressor units) on the prevention of histamine shock. Animals receiving one dog unit of suprarenal cortical extract subcutaneously and 10 c.c. of physiologic normal saline intraperitoneally three hours preceding lethal doses of histamine showed a delay to histamine shock of an average of one-half hour compared with the controls. They all died however in more violent shock than when treated with histamine alone. Animals, receiving one unit of posterior pituitary pressor extract three hours before receiving a lethal dose of histamine, showed either no evidence of shock or very slight shock.

Clinical observations, as well as these few preliminary animal experiments, would indicate that there is no rational therapy for the use of suprarenal cortex hormone in allergic states.

Posterior pituitary lobe extract, however, seemed to have an antagonistic action to histamine. An epinephrine-pituitrin compound is marketed in the belief that posterior lobe extract prolongs or enhances the action of epinephrine. Clinically the combination is sometimes more effective in asthma than epinephrine alone. This may be the result of an antagonistic action to histamine.

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*Torantil (Histaminase) in Urticaria, Following Serum Administration.* Toomey, J. H., Kriete, F. M., and Epstein, H. C.: J. Pediat. 24:290, 1944.

In their first experiment, the authors gave four tablets of torantil, four times a day, to thirteen patients who developed urticaria following serum administration. There was no change in the duration or severity of the symptoms between these patients and thirteen untreated patients. Similar control comparisons with increased dosage failed to show any material difference between untreated and treated cases. Thirty-six patients with epidemic meningitis, were given torantil as soon as the meningococcal serum was administered in treatment. Twenty-nine cases of epidemic meningitis served as a control. No patients were treated for less than eight days and the treatment was considered as being prophylactic and therapeutic. The authors concluded that Histaminase neither prevents nor ameliorates the serum sickness which follows the administration of meningococcus antitoxin.

# Editorial

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## INSTRUCTIONAL COURSE

The Educational Committee of the College will conduct its next biannual graduate continuation course in allergy at Northwestern University in Chicago. The course will extend from Monday morning, November 5, to Saturday noon, November 10. Lectures and demonstrations will begin at 9 a.m. and will continue until 6 p.m., with a recess of one hour at noon. Registrants may be members or nonmembers of the College. There will be an informal dinner on Monday evening, November 5, in order that the participants may become better acquainted.

Experienced instructors, outstanding in their respective fields, will conduct the courses. Their selection will be based upon the information furnished by the Speakers Bureau of the College and upon their experience in teaching, with an effort to rotate the instructors, when possible, considering those best qualified. The practical, clinically essential features of the various allergic diseases will be adequately presented, keeping in mind the postwar demand for increased knowledge of allergy by physicians in general, when assuming civilian responsibilities. The course will be sufficiently intensive for the advanced physician, wishing to refresh his knowledge of the subject, as well as practical for the newly qualified, desirous of applying proper allergic procedures to their practice.

Chicago, because of its central location, affords an excellent opportunity to medical officers interested in allergy as well as to Canadian physicians. There will be no charges to those in the armed service. The registration fee for others will be one hundred dollars.

All registrants will receive outlines of the courses as well as the revised Manual of Allergy Laboratory and Diagnostic Procedures.

A tentative schedule of the course is herewith presented. The complete course, listing the instructors, will be published in an early issue of the ANNALS. Announcements, including all details, will be mailed in the near future. In addition, announcements will be sent on request.

Registration should be made early, preferably by mail. Hotel reservations should be made in advance. All those wishing to register for this course will please communicate with the Secretary, American College of Allergists, 401 La Salle Medical Building, Minneapolis 2, Minnesota.

At this time the Office of Defense Transportation does not restrict meetings limited to an attendance of fifty. Therefore, it is urged that those contemplating attending the course register early.

If untoward circumstances prevent attendance, the fee will be refunded.

## EDITORIAL

### SCHEDULE

November 5-10, 1945

Inclusive

#### *Monday, November 5*

- 9:30 Registration.
- 10:00-11:30 Fundamentals of Allergy—Immunologic.
- 11:30- 1:00 Fundamentals of Allergy—Physiologic.
- 2:00- 4:00 Laboratory and Diagnostic Procedures—General Discussion.
- 4:00- 6:00 Laboratory and Diagnostic Procedures—Demonstration of Techniques.
- 7:30 Informal Dinner.

#### *Tuesday, November 6*

- 9:00-11:00 Histopathology of the Allergic Reaction.
- 11:00-12:00 Materia Medica of Allergy and Pharmacology of Drugs Used in Allergy.
- 12:00- 1:00 Allergy of the Nose and Paranasal Sinuses—Perennial Allergic Rhinitis (1st session).
- 2:00- 4:00 Allergy of the Nose and Paranasal Sinuses—Seasonal Allergic Rhinitis (2nd session).
- 4:00- 6:00 Serum Disease; Allergy from Drug and Biologic Products.

#### *Wednesday, November 7*

- 9:00-10:00 Physiology of Respiration.
- 10:00-11:30 Bronchial Asthma—General (1st session).
- 11:30- 1:00 Bronchial Asthma—Therapy, etc. (2nd session).
- 2:00- 3:00 Dermatologic Allergy—Atopic Dermatitis (1st session).
- 3:00- 4:30 Dermatologic Allergy—Urticaria (2nd session).
- 4:30- 6:00 Dermatologic Allergy—Contact Dermatitis (3rd session).

#### *Thursday, November 8*

- 9:00-10:00 Pediatric Allergy (1st session).
- 10:00-11:00 Pediatric Allergy (2nd session).
- 11:00-12:00 Pediatric Allergy (G. I. Allergy in Infants)—(3rd session).
- 12:00- 1:00 Pediatric Allergy (Skin Diseases in Children)—(4th session).
- 2:00- 5:00 Allergy of the Central Nervous System.
- 5:00- 6:00 Ocular Allergy.

#### *Friday, November 9*

- 9:00-11:00 Vascular Allergy.
- 11:00-12:00 Physical Allergy.
- 12:00- 1:00 Psychosomatic Allergy.
- 2:00- 3:30 Gastro-intestinal Allergy.
- 3:30- 4:30 Miscellaneous Allergies—Agranulocytosis (1st session).
- 4:30- 6:00 Miscellaneous Allergies—Joints, Urinary Tract (2nd session).

#### *Saturday, November 10*

- 9:00- 1:00 General Review and Round Table.

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### PROBLEMS TO BE CONSIDERED IN THE STANDARDIZATION OF ALLERGENIC EXTRACTS

At the recent meeting of the Board of Regents of the American College of Allergists, Dr. George E. Rockwell, Chairman of the Standardization Committee, gave a report on the progress of the committee.

In discussing the objectives and purposes of standardization, it was brought out in the Letters of the International Correspondence Club of Allergy, recently, that standardization is not of particular interest, but

"clinical dependability and results" are the factors. This seems confusing, for the whole purpose of standardization is just that: namely, standardization makes for consistent clinical dependability and results.

In the Letters the question was also raised why, since house-dust extract can be purified by precipitation with acetone, could not this method be employed for all allergens. Because the method is successful with dust does not mean that it is applicable to all substances. One questions whether milk extract could be so purified.

Purification, while certainly important, will not solve all problems and it alone will not lead to uniformity and dependability. Is there any evidence that even one company's extract is always consistently the same, bottle after bottle, year after year? Unless some method for standardization is developed the allergist has no assurance that he can buy a bottle of a given extract and use it exactly as he did its predecessor. He has no assurance that they are comparable in antigenic properties, activity, concentration and other factors; consequently he cannot be sure of clinical dependability and results.

Standardization of allergens to be successful will undoubtedly have to be done both biologically and chemically. The chemical standardization, if at all possible, should be put on a scientific basis such as normality, molar, oxidation or reduction capacity, et cetera.

Recently, the American Academy of Allergy voted to continue temporarily to use nitrogen as precipitated by phosphotungstic acid as a basis of standardization of pollen extract. At the same time they admitted that there are two or more antigens present in pollen extract, yet they endorsed a method of standardization which gives no information as to the amount of the various antigens present. A method of molar standardization has been suggested which will furnish such information, but apparently it was not even considered. The method itself is simple to use and requires only one more determination than the phosphotungstic acid method. It is only by trial and experiment that its value can be tested, its insufficiencies exposed and improvements made. This means that it will be necessary for allergists all over the country to co-operate in an effort to work out and try new methods if progress along this line is to be expected.

Two experiments of the Standardization Committee were offered to illustrate these points. In the first, a ragweed pollen extract was prepared by Doctor Rockwell which contained identically the same amount of total nitrogen as an extract used by the Army. However, the distribution of nitrogen between large and small molecular antigen was different in each extract. This is shown in Table I.

These extracts were then assigned by Major Halpin to four allergy clinics where they were tested on more than one hundred cases. It was found that the extract labeled Rockwell was considerably more potent than the extract labeled Army; that it gave larger skin tests and in more

# EDITORIAL

TABLE I

Extract	Total nitrogen mgs/c.c.	Army units	Molar Units		
			AMU (major antigen)	BMU (minor antigen)	TMU (total)
Army,	0.1000	10,000	892	13,923	14,815
Rockwell	0.1000	10,000	3,062	11,900	14,962

dilute concentrations. From this, it is evident that although two extracts have identically the same amount of total nitrogen, they are not comparable clinically. Therefore, total nitrogen is not a reliable criteria for standardization.

A similar experiment was done using two extracts which were identical in the amount of nitrogen precipitated by phosphotungstic acid, but which were not identical on the molar basis. They proved to be different clinically.

For the second experiment, two dust extracts were made which were identical in total nitrogen; but Extract A contained two and one half times as much precipitable nitrogen as did Extract B. Extract A gave skin tests in higher dilutions than did Extract B. Extract A was then diluted to contain the same amount of precipitable nitrogen as B and this was called Extract C. It gave reactions almost identical to Extract B. This is shown in Table II.

Thus we see that total nitrogen is not a criteria for the standardization of dust extracts, but precipitable nitrogen may be. Experiments are in progress which indicate that although precipitable nitrogen is more reliable than total nitrogen in dust extracts, it is not completely reliable in certain instances and molar standardization will probably be more applicable.

At this meeting the Board of Regents decided to intensify the studies on the standardization of dust extracts. To facilitate this a program was developed which includes three major points. *First*—A series of extracts will be prepared. These extracts will be made from dust collected from all parts of the country which will be extracted, preserved, purified and standardized by various means. *Second*—A committee consisting of Drs. Ethan Allan Brown, Fred W. Wittich and French K. Hansel was appointed to specify definitely the technique, interpretation and reporting of skin tests done on this series of extracts. *Third*—A group of doctors located all over the country will be selected to do these skin tests.

A diligent following of this program will yield sufficient data to be conclusive. It certainly warrants the co-operation and the consideration as well as the conscientiousness of all allergists. We all wish to



# EDITORIAL

TABLE II\*

Dust Extract	Nitrogen mg/c.c.	Precipitable nitrogen mg/c.c.	Skin tests on dust sensitive patients done by Dr. Wittich					
			Patient	Dilutions 1:				
				10	100	1,000	10,000	100,000
A	.370	.310	Mrs. B	++	+	+-	-	-
			Dr. C	+++	++	+-	-	-
			A. A.	++++	++++	++	-	-
			Dr. L	++++	++++	++	+	-
			C. S.	++++	++++	++	+-	-
B	.314	.124	Mrs. B	++	-	-	-	-
			Dr. C	++	+-	-	-	-
			A. A.	+++	++	-	-	-
			Dr. L	++++	+++	++	-	-
			C. S.	+++	-?	+-	-	-
C	.148	.124	Mrs. B	++	+-	-	-	-
			Dr. C	+++	+-	-	-	-
			A. A.	+++	++	-	-	-
			Dr. L	++++	+++	++	-	-
			C. S.	+++	++	+	-	-

\*Skin reactions were based on measured wheals and areas of erythema.

see this problem satisfactorily controlled, and the only way that this can be achieved is by dividing the responsibility between each and every one of us.

*Standardization Committee  
Advisory Council  
GEORGE E. ROCKWELL, Chairman  
J. WARRICK THOMAS  
FRED W. WITTICH*

## ORAL DE-ALLERGIZATION OF FOOD HYPERSENSITIVENESS

As indicated in a previous editorial, research in allergy must remain one of the most important interests of the College. New concepts are rightly or wrongly received with utmost skepticism, which, while often well founded, sometimes retards progress. The present generation, to which allergy is an accepted branch of medical science, does not know how the basic ideas of pioneers such as Bostock, Blackley, von Pirquet, Besredka and others in the beginning were ridiculed or even received with hostility.

In our time, too little basic research, particularly along experimental lines, is carried out, partly due, of course, to war conditions. For this

†Research in Allergic Disease, Ann. Allergy, 3:73, 1945.

reason we have approved the publication of a series of papers by Dr. Erich Urbach and his associates, who introduced the concept of de-allergization as an alternative to hyposensitization. On the basis of extensive animal experiments using the Schultz-Dale and the lung perfusion methods as criteria for the presence or absence of antibodies, Urbach postulates that it is possible to "de-allergize" animals highly allergized to proteins by the oral routes, using propeptans. These are specific food digests derived from individual food proteins by digestion with hydrochloric acid, pepsin and trypsin. They are free of native protein, rich in proteoses, contain a good proportion of peptones, as well as a small percentage of simpler nitrogen compounds.

Although in Europe the method was tried and advocated by a number of investigators, comparatively few allergists in this country, to our knowledge, have attempted to confirm the procedure, and some have had no success with it. Those of the latter group, who reported negative results, employed their own preparations, whereas the European group used the original propeptans. The editors of the ANNALS suggest an impartial inquiry of the method by experienced allergists, using the original propeptans, particularly by those allergists versed in the scientific study of food allergy.

The investigations should be made upon a sufficient number of definitely known food reactors as well as an equal number of unselected controls which would furnish sufficient statistics and which would be finally convincing of the relative value of the procedure. Urbach's insistence on the proper selection of cases and meticulous supervision of the patient's diet should be given due attention.

A sufficient number of satisfactory case records should be furnished by those undertaking the investigation of propeptans, whether their comments are favorable or unfavorable.

It may be made possible through research funds for those qualified to make the experiments to be furnished with the material for such a study. The results of these investigations, if sufficiently important, may then be published in the ANNALS.

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*A Note on Cysts and Abscesses Induced in the Rat by the Injection of Oils.* Emery, F. E., Matthews, C. S.: J. Lab. & Clin. Med., 28:1795, 1943.

One c.c. of oil was injected intramuscularly in the hind leg of a rat and the site examined two days to one year later for oil, hemorrhage, durability of cyst wall and abscesses. All oils tested (mazola, olive, cottonseed, sweet almond, sesame and peanut) formed cysts. Abscesses were present in nearly one-half of the rats injected with sweet almond oil and in a few with cottonseed oil. Aseptic technique had no bearing on the incidence of abscess formation. With thickness of the cyst capsule as an indicator, sesame oil is more irritating than mazola, olive and peanut oils. All four failed to induce gross inflammation. Sweet almond and cottonseed, therefore, were considered most irritating.

# Progress in Allergy

## A REVIEW OF THE LITERATURE FOR 1944

### Drugs

ETHAN ALLAN BROWN, M.R.C.S., (London) L.R.C.P., (England) F.A.C.A.

Boston, Massachusetts

Of the 700 papers published during the last year on the subject of Allergy, the following were chosen for their general interest. A good number of the papers not mentioned will be found in the specific subject reviews which are part of this same series and include the fields of Hay Fever, Bronchial Asthma, Atopic Dermatitis, Immunology, Pediatric Allergy, and Chemistry of Pollen. It is assumed that the majority of our readers are familiar with the papers published in the *ANNALS OF ALLERGY* and in the *Journal of Allergy*, and with few exceptions these also have purposely been omitted.

The general pattern of research in Allergy has changed little in the past year, but, although no major discoveries have been made, a number of problems of moderate stature have been solved and the field of Allergy presents fewer lacunae than it did several years ago.

Sensitivities to the sulfonamides are the subject of a number of papers. Goldschlag<sup>29</sup> reports that the local application of sulfonamides to dermatidites has provoked cutaneous and general sensitivities in about 12 per cent of his patients. He stresses the point that sensitivity to one sulfonamide is usually associated with sensitivity to others and that, in many of his cases, the later application of other drugs provoked a reaction similar to that produced by the sulfonamide. Goldschlag feels, as do many other dermatologists, that the topical application of sulfonamides is contra-indicated whenever other medications will serve the same purpose.

Fisher<sup>20</sup> treated more than 100 patients in whom local or general dermatitis occurred following the local application of sulphanilimide. In twelve of these, oral ingestion of sulphanilamide (0.5 gm.) caused a reappearance of the typical erythematopapular rash seen as a result of the original sensitization.

Lee<sup>42</sup> saw a single prophylactic dose of sulfadiazine (2 gm.) elicit a drug reaction in one hundred and twenty-eight of 25,000 patients. Despite the fact that only a single dose was given, three patients presented a hyperpyrexia accompanied by mental disturbance. In six additional patients, the symptoms lasted for three days for five patients and as long as two weeks for the sixth. In another fifteen patients there was conjunctival injection and a cutaneous eruption, and in one hundred others, mild general reactions which persisted for twenty-four hours.

In a patient reported upon by Koteen<sup>40</sup> a child sensitive to sulfadiazine developed a rash, hyperpyrexia, lymphadenopathy, hepatosplenomegaly, thrombocytopenic purpura and agranulocytosis, following the ingestion of sulfadiazine (9 gm.) of which detectable amounts were still present in the blood twelve days later. The patient recovered, although another patient who developed a similar thrombocytopenia was found to present massive hemorrhages in the adrenal glands, demonstrated post-mortem.

Reed<sup>60</sup> described sulphanilamide as causing convulsions and unconsciousness in a female child and Randolph and Rawling<sup>50</sup>, bronchial asthma as occurring in one patient who had had no history of either asthma or allergy and similar symptoms

following the ingestion of sulfadiazine in a patient who had previously suffered from atopic dermatitis, allergic rhinitis, and bronchial asthma. In both patients there was a diminution of vital capacity, and in each a recurrence of symptoms following a second ingestion of the responsible sulphonamide.

In a patient described by Zanfagna<sup>81</sup> there was not only bronchial asthma, but also edema, pruritis, and urticaria. The asthmatic symptoms persisted for ten days.

Abramowitz<sup>2</sup> lists the complications which may follow sulfonamide ingestion as (1) the development of a local or generalized dermatitis, (2) the appearance of photosensitization to ultra-violet radiation, (3) the interference of the action of Roentgen rays, (4) the delay in wound healing time, (5) local sanguineous oozing, (6) interference with the action of sulfonamide compounds by anaesthetics of the procaine series, (7) resistance to sulfonamide therapy, and (8) vulnerability of the patient to subsequent use of the same drug. He feels that the indiscriminate use of sulfonamides is questionable, not only because of the uncertain results but because of the potential hazards listed. His paper, well worth reading in full, reviews the literature pertaining to reactions of sulfonamide therapy and discusses both the histology and pathogenesis of the eruption.

Park<sup>83</sup> tables the reactions of patients to sulphanilamide, sulphapyridine, sulfaguanidine, sulfathiazole, and other sulfonamides. Of the forty patients described, twenty-four reacted only to the individual sulfonamides to which they were initially sensitized. No patient was allergic to more than one of the series without being allergic to them all, as well as to sulphanilic acid. Park concludes that the patient who is sensitive to one sulfonamide may be able to take another but if he is sensitive to two, he is probably sensitive to all. Park's papers on this subject are all well worth reading. In a letter to the *British Medical Journal*<sup>67</sup> treatment with nicotinic acid (50-100 mg.) is described as preventing toxic reactions to sulfathiazole in a patient in whom irritation of the hands, mouth, and anus followed the ingestion of the sulfonamide.

McCormich<sup>49</sup> feels that the improvement in his patient who had a sulfonamide sensitivity was due to the ingestion of ascorbic acid, of which 500 mg. was given daily for a week. The patient was also given oral vitamin B complex. He states that unfavorable skin reactions due to the sulfonamides may be partially related to ascorbic acid deficiency.

Not all forms of treatment with sulfonamides are associated with such sensitivities. Ballenger<sup>6</sup>, treated approximately 500 colds with a spray containing ephedrine (2 per cent), the nose then being sprinkled as extensively as possible with sulfathiazole powder. Only three patients developed a skin rash which disappeared within twenty-four hours. Those patients who were known to be sulfonamide sensitive were not treated. The author concludes that although an exact evaluation of the therapy is difficult, the course of the acute infection was shortened and the incidence of complications lessened. Cassady, discussing the paper, was of the opinion that the patients who used sulphathiazole preparations had more nasal congestion and greater irritation than those who use ephedrine alone.

Geiter<sup>26</sup> describes the characteristics and uses of a new salt formed by the chemical combination of neo-synephrine and sulfathiazole. It possesses vasoconstrictor properties comparable to equivalent amounts of neo-synephrine base and approximately the bacteriostatic action as the same quantity of sulfathiazole solution. The material was used in a 1% dilution during the first stages of common colds in several hundred steel workers who used the material twice or three times daily for two days. It was said that only two of the patients progressed to the secondary or muco-purulent stage of naso-pharyngitis. Clinically, there were said to be no symptoms of irritation or sensitivity.

Williams<sup>80</sup> of the Mayo Clinic feels that sulfonamide therapy is useful in acute

sinusitis but that the application of sulfonamides in solution with vaso-constrictors is contra-indicated. He recommends the use of the micro-crystalline sulfonamide suspensions. Weille<sup>78</sup> has used sulfadiazine in the 2.5 per cent solution in 8 per cent triethanolamine as a nasal spray in several hundred patients with no report of irritation or sensitivity.

It is only natural to expect that nebulized solutions of sulfathiazole would be used in the treatment of bronchial lesions. Applebaum<sup>5</sup> experimented with the inhalation of a 5 per cent nebulized solution of sulfathiazole sodium and discovered definite improvement in forty-three of fifty patients suffering from various types of bronchial infections. The patients inhaled approximately 2 c.c. of the solution for twenty minutes, three times daily for ten days. There were two patients who had mild, local, toxic reactions and for these, treatment by nebulizer was discontinued. Oatway<sup>52</sup>, on the other hand, treated forty-eight patients with purulent bronchial secretions, with sulfadiazine, sulphamerazine, and sulfathiazole, given orally. In all cases, the sputum was reduced, the average reduction being 62 per cent. The medication was more efficient in simple bronchiectasis than in the presence of atelectasis and putrid secretions. Eleven of the patients had bronchial asthma. In all of the patients the treatment was combined with postural drainage, bronchoscopic aspiration, climatotherapy and treatment of the sinuses.

Reports of penicillin sensitivity are rapidly becoming more numerous, as the drug becomes more widely used. Pyle and Rattner<sup>58</sup> describe a contact dermatitis which occurred in a medical officer who both prepared the various solutions and administered the penicillin to patients. His dermatitis began as a marginal blepharitis and conjunctivitis, and spread to the bridge of his nose, the forehead, and the central portions of his face. Over a period of several weeks eczematous lesions appeared on the hands and penis. As soon as the patient ceased handling penicillin, the eruptions disappeared, recurring as soon as he was re-exposed. Patch tests to penicillin were strongly positive while additional patch tests to the medium, on which the penicillin was cultivated, were negative.

A patient described by Silvers<sup>69</sup> worked as a chemist engaged in penicillin research. He also developed an itchy rash of the eyelids, and the penis, following approximately one year of exposure. A patch test with a pure sodium salt of crystalline penicillin was negative, whereas a similar test with the yellow amorphous form of penicillin sodium was positive. The rash disappeared as soon as direct contact with penicillin ceased.

The patients described by Binkley and Brockmole<sup>11</sup> were physicians administering penicillin to hospital patients. In the first, the eruption appeared on the forehead and lower arms and in the second, was thought to be a seborrheic dermatitis. For the first patient, a patch test with a solution of penicillin containing 5,000 units c.c. was strongly positive. For the second, the patch tests were negative, but an injection of 60,000 units caused pruritis and an eruption of the hands and feet. In both cases, the eruptions ceased when contact with penicillin was avoided. In Barker's patients<sup>9</sup> one, a medical officer dispensing penicillin solutions, the reaction was again an acute dermatitis of the face and neck with vesiculation and a serous exudate of the chin. There was edema of the upper and lower eyelids, subsiding as soon as the patient's occupation was changed. The second patient reported upon in the same paper, responded to penicillin injection with dermatographia and large confluent wheals on the trunk and extremities. On each patient, patch tests reproduced the original lesions.

The patient described by Freyhan<sup>23</sup> developed a severe generalized pruritis for five days, following the administration of 100,000 units of penicillin over a period of ten days. A patient as described by Criepp<sup>16</sup> developed a generalized urticaria following the injection of 200,000 units of penicillin over a period of fourteen days.

On this patient, direct intradermal skin tests, passive transfer and precipitin tests were positive to the penicillin drug solution. No anaphylactic antibodies could be demonstrated in the patient's serum to penicillin extract.

Animal experiments by McClosky and Smith<sup>48</sup>, using guinea pigs who were sensitized with small daily doses of commercial penicillin, proved sensitivity to be present by both the intracardiac and intravenous injection shocking method and by tests upon the isolated uterus. Sensitization, however, was not uniform in that independently of the doses (5,000-23,000 units) some animals died and others showed no response. The uterine response was often delayed. Desensitization was difficult to demonstrate.

Putney<sup>57</sup> describing the use of penicillin in diseases of the nose and throat, feels that penicillin therapy is the best means of combating infection in these areas. Of nine patients with orbital cellulitis, or brain abscess, only one failed to respond. In chronic osteomyelitis of the frontal bone, lengthy penicillin therapy usually eliminates the necessity for surgery, but in one patient, over 7,375,000 units given over a period of 66 days failed to overcome infection. Acute maxillary sinus infection was cured after several irrigations with penicillin solution. Eight patients with sinus thrombosis adequately treated with penicillin made an uneventful recovery from operation. Used alone, penicillin was disappointing but when combined with adequate drainage as obtained by surgery it effected cure in the majority of patients treated.

Thiamine continues to be the subject of reports on sensitization. A patient treated by Stein and Morgenstern<sup>72</sup> became sensitized so that following the eighth of a series of subcutaneous injections of 30,000 I.U., he suffered for 24 hours from pruritus, dyspnea, and cyanosis. In a patient treated by Mitrani<sup>50</sup> each of six injections with 50 milligrams of thiamine hydrochloride was followed by a maculo-pruriginous eruption of the face, chest and back. Cutaneous tests and passive transfer tests were positive. The patient was successfully desensitized by daily subcutaneous injections, so that eventually he took with no reaction, 100 milligrams daily for ten successive days. Following the course of desensitization, the intradermal tests are said to have become negative.

Reports of dermatitis due to the barbiturates are common but it is comparatively rare to find the condition associated with a progressive anemia. Potter and Whitacre<sup>56</sup> noted a temperature rise and marked erythema covering the entire body following the administration of luminal (1.5 gr.). The next day, following a second dose, the erythema became more pronounced. The patient received Amytal (1.5 grs.) and Aminopyrine (3.5 grs.) which was followed by a chill, with further rise in temperature and the appearance of serous-filled blebs covering the entire body. During the next seven days the red cell count declined to 3,000,000 and the hemoglobin to 58%. The skin presented large indurated areas and desquamation. The patient eventually recovered.

For the many plants listed as causing contact dermatitis must be added those to which members of Armed Forces, in their new geographical environments, are being exposed. Hitch<sup>36</sup> describes a severe dermatitis venenata resulting from contact with the Acajou tree (*semecarpus atra*) which occurs in New Caledonia, the Loyalty Islands, and the New Hebrides group. Nine of ten volunteers who were subjected to study, passed through the typical stages as observed among the patients, the incubation period being two to five days.

Satulsky<sup>64</sup> had previously described dermatitis venenata as caused by the Manzanillo tree with which contact occurs in Panama and the Canal Zone. Harley<sup>33</sup> reports on the severe keratoconjunctivitis and dermatitis due to contact with the Manzanillo tree agreeing with the previous author in stating that effective therapy consists of the prompt use of saline solution. Experiments on rabbits showed that saline irrigation, five minutes after eye contamination, would reduce but did not

prevent the keratoconjunctivitis. On humans, the sap left on the skin for thirty minutes could be removed effectively by ether, soap and water, sea water and lime juice. Oil from the Bhilawanol tree which is related to the cashew nut tree caused an acute dermatitis in sixteen subjects studied by Goldsmith.<sup>31</sup> The patients had come into contact with a mail pouch shipped from India over which the material had been accidentally spilled. Patch tests to the contaminated paper were positive in an unexposed subject. Also from India, Livingood and his associates<sup>46</sup> report on Dhobie mark dermatitis of which there were fifty-two cases in the Twentieth General Hospital, following the wearing of clothes which had been marked with this material derived from the Bella Gutti tree. Patch tests were positive in 80.5 per cent of the subjects, the remainder giving positive tests to marking fluid prepared from the green nuts.

Here at home, Steele and Sawyer<sup>71</sup> remind us of the immediate, severe, generalized urticaria which develops from contact with the brown-tail moth. This insect feeds chiefly on the foliage of apple trees, but is also present in oak, willow, and other common hardwood trees and shrubs. Poisonous material from the caterpillar, the adult moth or the nests coming into contact with human skin produces an urticarial response. Injections at five-day intervals over a period of several months resulted in desensitization.

Two extremely common substances causing allergic reactions are described, first, by Parkin<sup>54</sup> whose patients presented dermatitis due to daffodil juice and second by Sterling and Hollander<sup>73</sup> a case of bronchial asthma due to sensitivity to aspidistra. Tabershay and Skinner<sup>77</sup> report on an eczematoid dermatitis which developed in fourteen of thirty subjects exposed to vinyl carbazole used for impregnating electrical equipment. In another plant all individuals in contact with this material developed a dermatitis within five to fourteen days following exposure.

This last year has brought forward the usual crop of new nasal vasoconstricting agents and the usual reports of the deleterious effects of those introduced the year before. Sternberg<sup>74</sup> reminds us that vasoconstrictors should be used only in nasal sprays and never in the form of drops and should be applied, at the most, once or twice daily preferably when the symptoms are most severe. When used too frequently the mucous membranes become refractory and remain irritated, inflamed, and water-logged. Kully<sup>41</sup> also stresses the point that nasal vasoconstricting preparations have a second dilating effect and that the severity of this secondary congestion is proportional to the frequency with which the preparation is used and the intensity of the vasoconstriction. He also feels that the incorporation of sulfonamides usually causes a severe irritative congestion. He lists the indications for the various medications giving the effect of each on the nasal mucosa and cilia and discussing their therapeutic value.

In 1943, Fabricant and Van Alyea<sup>19</sup> evaluated Privine, which in 104 subjects produced neither local nor general mucous membrane side effects. Gallom<sup>24</sup>, however, reported that the use of Privine (0.1 per cent) solution produced toxic reactions in the nasal tissues. In four of his patients, each of whom obtained relief when first using the drug, progressively increasing amounts were soon required. When the drug was discontinued, the nasal congestion rapidly disappeared of its own accord. The present author's personal experience with Privine corroborates the fact that the patients do require more and more of it as they use it due to the secondary action of the drug itself and not to any exacerbation of the primary allergic condition.

Of fourteen patients treated with local application of Neo-Synephrine by Saltzman<sup>63</sup> a 0.25 per cent solution relieved eight, the remaining six requiring a 1% solution of the drug. In another patient there was a rise in systolic pressure as well as a severe occipital headache, stiff neck, vomiting and profuse perspiration.

Vonedrine (phenylpropylmethylamine) has been the subject of clinical study by

Bumgardner and his associates.<sup>13</sup> They used the substance combined with levulinic acid, Ceepryn and Chlorobutanol in an isotonic solution with a pH of 5.5. The patients, of whom there were 150, suffered either from acute rhinitis, acute sinusitis, chronic sinusitis or allergic rhinitis. The material was used as a spray, as swabs, or as tampons. It was ineffective in allergic conditions. The results were poor in acute or chronic sinusitis. In no patients were there troublesome systemic or side reactions. In our own experience Vonedrine has not given good results in nasal congestion nor has Ceepryn shown itself to be antiseptic.

Stitt<sup>75</sup> on the other hand used the material successfully in 250 patients over a period of forty months. Using a nasal wick technique he reports good results in shrinking the nasal mucosa and opening the ostia of the sinuses. There were no toxic reactions. Vonedrine has also been used by Glaser<sup>28</sup> in ten cases of bronchial asthma of whom six improved when taking in oral doses (25 mg.) several times daily from five to six months. In seven patients the blood pressure remained constant and in three, decreased. There were no symptoms of central nervous stimulation or disagreeable side effects. The author feels that the drug is as effective as ephedrine and less disturbing than either ephedrine or epinephrine although not as efficient in its broncho-dilating properties as epinephrine.

Marvin<sup>47</sup> used Propadrine pre-operatively in 750 patients, injecting the material subcutaneously in doses of 50 mg. with 2 c.c. of procaine solution (1 per cent). Vasoconstriction is reported to have been satisfactory, the cases including patients who suffered from hypertension, diabetes and heart disease. The drug is said to be more active and less toxic than ephedrine and unlike epinephrine does not cause cardiac irregularities.

Hansel<sup>32</sup> prescribed Nethamine and theophylline isobutanolamine for nasal allergy and bronchial asthma in 200 adults. The drug can be used intramuscularly or intravenously, in severe asthma. Rectal suppositories were also satisfactory. Nausea and vomiting followed oral administration less frequently when the drug was given with food or as an enteric-coated capsule. Whenever the intravenous injection was too rapid there were sensations of heat and burning, fullness of the head and chest, headache and occasional nausea. For the intravenous injection of 50-100 c.c. of the solution at least thirty minutes should be taken.

From England comes the report of a new drug, Pethidine, which, given subcutaneously by Douthwaite<sup>17</sup> in doses of 100 mg., relieved stubborn asthma when continuous treatment with epinephrine had failed. Within a month, Hobbs<sup>37</sup> described the ill effects of the same drug which had been used for persistent urticaria in a patient who treated herself with injections of 50 mg. three times daily for several months. She became excitable, talkative, completely irrational and disoriented. After the drug was discontinued and sedative therapy given, recovery was gradual.

A new drug for the treatment of bronchial asthma is described by Suter and Ruddy.<sup>76</sup> This preparation 1-(3, 4-hydroxyphenyl)-2 amino-1-butanol is said to be as effective as epinephrine in relieving acute attacks of bronchial asthma and yet does not excite the central stimulation nor raise systolic blood pressure. It seems to produce fewer side effects and is approximately one-hundredth as toxic as epinephrine. The diastolic blood pressure is lowered, the pulse rate is increased, the circulation improved without increase in cardiac effort. The dose required is 50 per cent greater than the aqueous solution of epinephrine, 1:1000. On the basis of this work it would seem that a new and effective drug for the treatment of bronchial asthma may soon be available for general use.

The story of Allergosil is now generally known. Smith<sup>70</sup> reported that in 413 patients, an average of three injections of 2 c.c. of the substance, ethylene disulfonate, gave complete relief in 76 per cent and partial relief to the remaining patients representing allergic states. In guinea pigs sensitized to egg albumin, Fisk, Small,



and Foord<sup>22</sup> found that, when three hours before the shock dose, some of the animals were given subcutaneous, intramuscular, or intraperitoneal injections of ethylene disulfonate, the mortality rates were 61 per cent for thirty-three animals treated with Allergosil, 68 per cent for thirty-one animals treated with water and 72 per cent for twenty-five untreated animals. The statistical analysis of these mortality rates showed the differences to be within the limits of standard error. The authors conclude that Allergosil does not protect guinea pigs against anaphylactic shock.

Publicity is still being given to the treatment of bronchial asthma with ascorbic acid. Although previously discussed in this journal, the subject merits brief review. In France, in 1938, Higiesco<sup>35</sup> reported that the intravenous administration of 300 mgs. followed fifteen minutes later by a second injection of 100-200 mgs. of ascorbic acid produced favorable results in sixteen cases of intractable bronchial asthma, only four patients not being benefited by the treatment. In the same year, Hunt<sup>39</sup>, in England, gave ascorbic acid orally to twenty-five asthmatic patients daily for eight weeks, five patients receiving massive doses parenterally, intramuscularly, and intravenously. There was no improvement in the incidence of attacks or in the general condition, nor was there any diminution in the amount of epinephrine necessary to relieve any attack. In the next year, Cintra<sup>14</sup> reported on twenty patients for whom he considered vitamin C as of considerable value, but Abatte (1) reported that in his patients 100 mgs. or more had no effect, excepting in the presence of vitamin C deficiency.

In 1943, Holmes<sup>38</sup> gave twenty-five patients suffering from ragweed hay fever 100 mg., 200 mg., and 500 mg. amounts of vitamin C during the ragweed season. Five patients were improved within one week while on the first dosage, sixteen showing no relief and serving running controls for the larger doses. Twelve patients improved after one week of 200 mg. taken daily and eight, after three or four days of 500 mgs. taken daily. In all, 88 per cent of the patients were said to have shown improvement. In addition, one asthmatic patient was greatly benefited by 500 mg. daily for two weeks and one eczema patient "almost cured" after one month of daily doses of 150 mg. In the following year, however, Hebal<sup>34</sup> reported on ten patients who were given 250 mgs. of ascorbic acid, twice daily for three or four weeks. Two patients reported slight improvement; eight obtained no benefit.

The effect of the ingestion of large amounts of ascorbic acid taken over a period of several days on skin tests was shown by Newbold<sup>51</sup> to be without significance. In eight male subjects the size of the skin test was unchanged. Englesher<sup>18</sup> gave 500 mgs. daily to forty-eight patients with both hay fever and asthma. He concludes from his preliminary findings that there is no reason to recommend the ingestion of vitamin C in pollenosis either as the sole measure of therapy or in conjunction with injection therapy.

Bowen<sup>12</sup> treated twenty-five patients with 600 mgs. of ascorbic acid daily and found no improvement as compared to twenty-five other patients who were treated without vitamin C. In the present author's own series (unpublished data), forty-eight patients were given 1,000 mg. daily over a period of two weeks during the height of the ragweed-pollen season. Twenty-three patients stated that they were slightly improved and the remainder that they were slightly worse. It is, of course, possible that only those patients with deficiency states are benefited.

Goldsmith and her associates<sup>30</sup> studied vitamin C nutrition in thirty-two patients of whom twenty-nine had bronchial asthma, two, hay fever, and one, urticaria. A subnormal level of ascorbic acid was found to be present in twenty-one patients. Nine of the patients were put on a standardized regime to determine whether or not they presented an increased need for vitamin C. Six of the seven patients with bronchial asthma were said to be unable to maintain as high a level of the

ascorbic acid as the control group could, under the same regime. In two of the patients the attacks were unaffected although the patients were saturated with ascorbic acid.

Since lowered capillary resistance is said to indicate ascorbic acid deficiency the work of Scarborough and Gilchrist<sup>65</sup> is of special interest. Data obtained from 214 simultaneous determinations did not support this point of view; the lower levels of resistance being found in the subjects with the greater plasma concentration of ascorbic acid.

The difficulties in assessing the papers listed lie in another field of science. The known relationships between calcium, protein metabolism and ascorbic acid have been ignored by almost all of the authors quoted. Crucial experiments definitive in scope and taking all of the various factors into consideration will be required before the true value of ascorbic acid in allergic states can be resolved.

The work with histamine in allergy continues apace. Gant and his colleagues<sup>25</sup> give histamine orally for the treatment of vasomotor rhinitis. It is of interest to note in a paper by Gibertini<sup>27</sup>, in 1942, that the saliva contains a large amount of histamine, although very little is present in either bile or gastric juice. It should be interesting to speculate on the mechanism by means of which oral histamine accomplishes its purposes.

The metabolism of histamine is receiving increased attention. The work of Alexander<sup>3</sup> shows that more than 60 per cent of the total amount of histamine present normally in mice is contained in the skin. The substance is excreted in the urine only when histamine concentration in the body is quite high. Whenever the concentration falls below a very definite level, some of the histamine appears in the urine but is evidently cleared through some mechanism other than renal channels. Intravenous injection (3 mg.) results in the excretion of large amounts of histamine in the urine and little in the feces. The histamine content of the blood becomes normal within twenty-four hours.

Those interested in histamine metabolism should read the papers by Anrep and his associates<sup>4</sup>, especially for their method for the quantitative estimation of histamine in the urine. They show that histamine can be eliminated both in a free and in a conjugated form. The first, typical of herbivora and the second, of carnivora. In the rat, both forms are present in proportions which vary. The ingestion of meat considerably increases the amount of conjugated histamine excreted. Histamine taken orally is eliminated in the conjugated form for about 5 per cent of the amount ingested. Injected histamine is eliminated in small amounts as the free form.

Roche e Silva<sup>61</sup>, knowing that previous investigators had shown that amino acids such as arginine, histidine and cysteine could block the effects of histamine upon isolated smooth muscle preparations, postulated that the imine group in the amino acids competed with the imine group in the imidazol ring of the histamine for the chemical receptors of smooth muscle. The author synthesized a number of histamine compounds in which the free amine group was combined with the carboxyl group of the various amino acids. These new compounds were devoid of histamine effects and yet were able to block the effect of histamine, added subsequently. The results were consistent with the theory that the pharmacological effects of histamine depended upon: first, the ability of the imine group in the imidazol ring to anchor cell receptors, and secondly, the toxic effect of the free amine radical. The quantities necessary, however (arginine 250 mg. for histamine 1 mg.), would discourage the anti-histamine effectiveness of these compounds in intact animals.

From the clinical point of view, Ruskin<sup>62</sup> has written an interesting and suggestive paper on the therapeutic use of the amino-acid histidine in allergy and shock, remarking on it as a factor in histamine-epinephrine balance. From the

physiological facts available it would seem that histidine treatment had a more rational basis than either treatment with histamine, free or conjugated, or with histaminase.

A measure of the complexity of this subject is seen in the work of Parrot and Richet<sup>55</sup> on the serous exudates of patients with active tuberculosis, acute gastric duodenal ulcers, malignant septic infections and typhoid fever. These workers discovered an organic vasodilating substance which differed from histamine and from acetylcholine. The compound which is more stable than acetylcholine and less stable than histamine produces hypotension and renal vasodilatation in anesthetized cats and dogs. It is soluble in water, ethyl alcohol and amyl alcohol and acetone, and insoluble in ether, chloroform, benzine, and petroleum ether. It is stable in acid and can be stored for several months in a 30 per cent aqueous alcohol solution at room temperature. Half the amount of the substance present is destroyed by human blood serum diluted 1-1-0 at a pH of 7.4 in fifteen minutes at 10° C. The authors state that the new substance described is likely to interfere with the determination of histamine and particularly with that of acetylcholine, since its presence in body liquids may have led to the overestimation of the vasodilator activities of acetylcholine as well as to the inflammation-producing properties of histamine.

Histamine itself is still being used for the treatment of a variety of conditions. Williams<sup>79</sup> treats intrinsic allergy as it affects the ear, nose and throat with subcutaneous injections of 0.1 c.c. of histamine diphosphate solution equivalent to a 1:500,000 dilution of histamine base. Doses given twice a day subcutaneously are increased by 0.1 c.c. each injection until symptoms disappear. A maintenance dose thereafter is 50 per cent of the dose at which improvement took place and average 0.6 c.c. of a 1:10,000 dilution of the histamine base. In some of the patients symptoms return six months after treatment is discontinued. Although some patients can only tolerate as little as 0.1 c.c. of a 1:200,000 dilution initially, no untoward symptoms occurred. The author states that injections of nicotinic acid (25-100 mg.) given subcutaneously in two days; and 100 mg. daily subsequently is as effective in vasomotor rhinitis, as is histamine. Two of his patients, not affected by either drug given alone were improved when both were administered together. In sixteen patients, nicotinamide was ineffective.

Lillie and his colleagues<sup>45</sup> used histamine therapy to improve the hearing of patients suffering from Ménière's syndrome. In twelve of twenty-five patients, the treatment consisted of the daily intravenous administration of a 0.275 mg. of histamine diphosphate in 250 c.c. of saline dextrose or potassium chloride solution given daily for three to six days at the rate of twenty to sixty drops per minute. Histamine was also injected subcutaneously in doses of 0.2 c.c. of a 1:10,000 dilution, increased by 0.05 c.c. twice daily until the patient took 1 c.c., or the optimal dose was reached. Injections were thereafter given daily but the amounts decreased according to the patient's response. In six patients there was marked improvement; in three, a moderate improvement, and in another three, only slight effects. Only three of the patients developed a subsequent increase of deafness. The patients given histamine in potassium chloride solution showed the greatest improvement in hearing, with the tinnitus disappearing in two, and being greatly improved in eight. In ten patients, there was no change. In nineteen patients the vertigo completely disappeared, and in two was greatly improved. In two patients there was no effect. In those patients, in whom symptoms recurred, they reappeared following acute upper respiratory tract infections.

Since histaminase is still being used clinically, a paper by Lemley and Laszkowski<sup>44</sup> on the action of this substance, *in vivo*, is well worth notice. They conclude from their work that histaminase in its present state of purity is toxic and that the dose cannot be increased to a level which would protect safely.

With the great interest in histamine azo-protein as a nonspecific method of treatment, mention must be made of the work by Cohen and Friedman<sup>15</sup> on immunity against H-substance. Patients, who, before treatment with histamine azo-protein, reacted to histamine given iontophoretically in a dilution of 1:6,400,000, reacted subsequently to a dilution of 1:200,000-1:1,600,000. These investigators conclude that histamine azo-protein presumably protects against the H-substance released in allergic reactions. Although the authors mention no untoward reactions in the patients treated with histamine azo-protein, in the present author's hands a number of reactions have occurred and similar reactions encountered by other investigators will soon appear in the literature of Allergy.

In this regard it is interesting to note the great gap which exists between clinical papers and the advertising claims based upon them. Hapamine (histamine azo-protein) is presented to physicians as intended for "the treatment of certain allergic conditions in which (1) the allergen is not discoverable, (2) complete avoidance of the allergen cannot be obtained (3) specific treatment with the allergen, in addition to avoidance, fails to restore tolerance levels, or (4) the allergen is of such nature that treatment is ineffective;" in other words, when the allergen cannot be discovered, cannot be used for treatment, cannot be avoided, or when the patient does not improve despite both treatment and avoidance.

It is obviously then no longer necessary to search for the specific causative allergen or having found it either to treat with it or have the patient avoid it. If the material works under these conditions it should undoubtedly work much better when, as in pollinosis, the allergen is known, and when the patient improves with either treatment or avoidance, or both. Since so little treatment is required over so short a space of time one wonders whether, ethically one should use anything else. If Hapamine does what it is claimed to do, treatment with Hapamine will assuredly replace all of our present diagnostic and therapeutic procedures. One eagerly awaits those reports which will certainly soon appear on the results achieved in hay fever. Since the material is also advertised as indicated in "contact dermatitis, physical allergy, urticaria, histamine headache, atopic eczema, vasomotor rhinitis and bronchial asthma" the review of the literature for 1945 should be interesting indeed and well worth waiting for.

Granted that histamine is the causative agent, the work of Lehmann and Young<sup>13</sup> should lead to important clinical data. These investigators discovered that diethylaminoethyldihydroanthracene carboxylate gave sensitized guinea pigs 100 per cent protection against one fatal dose of antigen. Diethylaminoethylxanthene carboxylate was 70 per cent effective. Diethylaminoethylfluorene carboxylate, aminophylline and epinephrine protected only 37 per cent of the sensitized animals. The first product listed above reduces the volume but not the acid concentration of histamine-induced gastric secretion. It intensifies the skin reaction produced by histamine injected intradermally. It reduces the resistance of the pulmonary circulation of the perfused guinea pig's lung as caused by histamine or anaphylactic reaction. It is a more potent broncho-dilator than aminophylline which, the authors suggest, acts beneficially in bronchial asthma because it lowers the resistance of pulmonary circulation.

To return to other forms of treatment, a case report by Fowler<sup>21</sup> presents several interesting facts. Following the removal of the left stellate ganglion, his patient presented a stoppage of the left side of the nose with watery secretion and much sneezing. Ephedrine, epinephrine, and cocaine were ineffective. Atropine sulphate (0.2 mg.), three hourly, had to be discontinued because of the general reaction. On the other hand, Syntropan (100 mg.) given orally three to four times a day, controlled the discharge and had no unpleasant effects. The patient continued with less medication until she was taking 100 mg. daily, continuously ingested over a period of two years.

The treatment of irritative cough of nasal origin by sino-nasal anesthesia is described by Bernfeld<sup>10</sup> who used pledgelets soaked in equal parts of pontocain (2 per cent) and epinephrine (1:1000) applied to the inferior and middle meati for ten minutes. Following this, epinephrine (1:1000) and novocaine solution (1 per cent) were used to infiltrate the tissues submucosally or subperiostally. The anterior and medial walls of the maxillary sinus were flooded with the anesthetic. The treatment, usually repeated, two to four times, gave lasting remission or great improvement.

Although the treatment of severe bronchial asthma is given great attention, surprisingly few references are made to the use of carbon dioxide inhalation. Holinger and his associates (*J.A.M.A.*, 117:675, 1941) found it to be the most effective of all expectorants. Banyai and Cadden<sup>7</sup>, evaluating its use over a period of thirteen years state that it changes an excessive but unproductive cough into a useful cough since it liquefies mucopurulent bronchial exudates reducing their viscosity. With the ensuing evacuation of the bronchi, the patient is free from annoying cough for comparatively long periods. The patient is treated for five to fifteen minutes, one to three times daily with 10 per cent carbon dioxide and 90 per cent oxygen set for a flow of four to five liters each minute for the closed method.

The treatment of bronchial asthma of the intractable type is the subject of a detailed paper by Barach.<sup>8</sup> The program for repeated bronchial relaxation consists of aminophylline (0.5-0.7 gm.) instilled rectally with 20 c.c. of water, twice daily for five days and then nightly for three weeks to three months. In refractory patients, 0.48 gm. of the drug is injected intravenously once daily. At intervals of four to eight hours, the patient is given 1 per cent epinephrine or vaponephrin by inhalation and if necessary epinephrine 1:1000 (0.5-1 c.c.) subcutaneously.

Concurrently a saturated solution of potassium iodide in doses of 1 c.c. three times daily is given orally for one week and then 0.3 c.c. twice daily. The patient is also treated with dilaudid 1/20th of a grain daily for four to five days, and if still refractory, is given intravenous glucose (50 per cent) 50 c.c. or 50-90 c.c. of ether in oil rectally. Phenobarbital 0.1 gm. is also given by mouth.

This program is supplemented by the inhalation of helium 75 per cent and oxygen 25 per cent for two hours twice daily. If the patient suffers from chronic bronchitis he, in addition, takes sulfadiazine orally. It would be an interesting study in pharmacodynamics to work out in detail, the actions of each of the drugs given and the methods by which it works. Fortunately, very few patients require such desperate treatment for relief of their symptoms.

Segal<sup>66</sup> used inhalational therapy in forty-nine patients with respiratory disease. Of these, twelve died, eight of whom presented conditions proven by autopsy to have been hopeless as regards treatment. When the patient's chief symptom was anoxia, he was given oxygen. If bronchial spasm predominated he was given helium (70 to 75 per cent) and oxygen (25 to 30 per cent) given under positive pressure. Repeated bronchial relaxation was accomplished by the use of rectal aminophylline, dilaudid, iodides, Neo-Synephrine and Vaponephrin nebulization with adequate humidification. Although Barach<sup>8</sup> finds sulfadiazine given orally more effective than the inhalation of nebulized sulfadiazine spray in Ethanolamine, Segal feels that the ideal technique in a patient with chronic bronchiectasis comprises nebulization with a micro-crystal suspension of sulfathiazole to which may be added iodides in addition to the use of oral iodides. Bronchoscopic drainage is periodically performed.

It may be inferred from this brief general review that each year sees our field become greater in scope and more varied in character. Contributions in the basic phenomena come more and more often from the fields of physics, physiology, immunology, biological and colloid chemistry. Since many of the papers do not appear in journals abstracted from the Cumulative Index, studies of the back-

ground literature must now include Biological Abstracts and the Abstracts of the American Chemical Society. A number of clinical papers, otherwise excellent, are marred by the fact that the authors were apparently not cognizant of the relevant material in the nonmedical literature and neither mentioned it nor took it into consideration. Our clinical papers can approximate the truth and attain permanent value only as they rest as firmly as possible on a solid scientific basis.

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# THE Rh FACTORS IN RELATION TO CLINICAL MEDICINE

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In 1940, when Landsteiner and Wiener<sup>10</sup> reported the discovery of the factor Rh of human blood, they opened a new chapter in clinical medicine. In searching for new properties in human blood, they injected the blood of rhesus monkeys into rabbits and obtained antisera which agglutinated the bloods of 85 per cent of white individuals in New York City. The new property in human blood was designated "Rh" (first two letters of the name Rhesus) to indicate the manner in which it had been discovered. Individuals whose red blood cells are agglutinated by the anti-rhesus sera are said to be Rh positive; those whose erythrocytes are not clumped by such sera are said to be Rh negative.

Shortly after the Rh factor was described, Wiener and Peters<sup>26</sup> presented the first evidence of its importance in clinical medicine. They described three cases in which patients receiving transfusions of blood of their own group had severe hemolytic reactions, one of them fatal.

In analyzing the cause of these reactions, they had first to overcome a mental hazard which had retarded progress in this field previously; namely, the rather general conviction that hemolytic reactions could not occur when patient and donor belong to the same blood group.\* To establish the diagnosis of intragroup hemolysis several days after a blood transfusion had been given, Wiener and Peters made use of a special technique, designated by them as "differential agglutination." This test, useful whenever post-transfusion hemolysis is suspected, takes advantage of the fact that the agglutinogens M and N are disregarded when selecting donors for transfusions.† If the donor and patient belong to different M-N types, then it is possible to trace the donor's blood in the patient's circulation because the M and N agglutinogens act as natural markers. For example, if the patient belongs to type N and the donor to type M, then after the transfusion the patient's circulation should contain a mixture of bloods of types M and N. Tests of the patient's blood suspension with anti-M serum should show clumps of cells (the donor's type M cells) on a background of unagglutinated cells (the patient's type N cells). If no clumping occurs this proves that the donor's cells have been eliminated and establishes the presence of a hemolytic transfusion reaction.

Having proved by the method of differential agglutination that intragroup hemolysis had indeed occurred in their cases, Wiener and Peters<sup>26</sup> sought the cause of the reactions. By a delicate technique they detected the presence in each patient's serum of an irregular agglutinin which agglutinated a certain proportion of blood suspensions of each of the four groups.\*\* By parallel tests, they then showed that all three agglutinins had identical specificities and gave approximately 85 per cent positive reactions. This suggested that the property responsible for the reactions was Rh, and parallel tests with anti-rhesus sera proved this assumption to be correct. Moreover, all three patients were shown to be Rh negative while the donors responsible for the reactions were all Rh positive.

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\*This belief prevailed even though a number of well authenticated cases had been reported of hemolytic reactions following transfusions of blood of the patient's own group. In a number of cases (Zach<sup>40</sup>, Culbertson and Ratcliffe<sup>4</sup>, Neter<sup>21</sup>, Levine and Stetson<sup>12</sup>) irregular isoagglutinins were detected in the patient's serum. However, no attempt was made to correlate these observations with one another, and the discovery of the Rh factor finally supplied the key to this transfusion problem.

†M and N are disregarded because they hardly ever give rise to transfusion reactions. Among hundreds of thousands of bloods tested, only 5 have been found with natural anti-M agglutinins, while in two additional cases anti-M agglutinins developed by isoimmunization following blood transfusion; no individual has been encountered in whom anti-N agglutinins were demonstrated with certainty (Wiener<sup>30</sup>). Only a single case of transfusion hemolysis has been traced to the M factor (Broman<sup>2</sup>).

\*\*See footnote, page 230.



Within a year, Wiener<sup>27</sup> collected ten additional cases of transfusion hemolysis due to the Rh factor, and it became clear that at least 90 per cent of intragroup hemolytic reactions could be explained on this basis. For those concerned with blood transfusion, the following facts are important to know:

(1) Natural sensitivity to the Rh factor has never been convincingly demonstrated in man. Therefore, the first transfusion of Rh-positive blood into an Rh-negative patient would not be expected to cause any reaction. This statement holds true universally among males, but there are exceptions in females as is explained below. At any rate, medical officers need not have any concern regarding reactions due to the Rh factor when transfusing wounded male members of the armed forces for the first time.

(2) When Rh-negative individuals are repeatedly transfused with Rh-positive blood a certain number of them will become sensitized to the Rh factor. In these patients transfusion reactions will occur which are usually mild at first (slight chilliness, or rise in temperature), then progressively become more severe, until finally a violent or even fatal hemolytic reaction will result. Fortunately, the vast majority of Rh-negative patients do not become sensitized despite repeated transfusions; in fact, only one in 25 to 50 Rh-negative individuals are readily sensitized by exposure to the Rh antigen. (This complication will not occur if the transfusions are given at short intervals, because it takes at least 5 to 7 days and usually much longer for sensitivity to develop.) It is obvious, therefore, that whenever transfusion reactions occur, no matter how mild, tests for the Rh factor should be carried out, in order to forestall a more dangerous reaction should it become necessary to repeat the blood transfusions.

(3) In testing for the presence of Rh sensitization, the usual procedure is to examine the patient's plasma for Rh isoagglutinins, as in the original investigations of Wiener and Peters.<sup>26</sup> Wiener<sup>27</sup> soon encountered some cases in which the patients were markedly sensitized, as proved by the occurrence of violent intragroup hemolytic reactions, yet their sera contained no detectable isoagglutinins. These apparently paradoxical cases have now been explained, at least in part, by Wiener's discovery of the Rh blocking isoantibodies.<sup>37</sup> These antibodies are so named because they combine specifically with Rh-positive erythrocytes without producing any visible reaction except that the erythrocytes lose their capacity of being agglutinated even by potent anti-Rh sera, due to blocking of their Rh agglutininogen. In effect, the Rh-blocking isoantibodies "convert" Rh-positive cells into Rh-negative cells. Recent studies suggest that the Rh-blocking isoantibodies are of greater clinical significance than the Rh-agglutinating isoantibodies, and the blocking test is already being used widely as a method of detecting Rh sensitization.

The final test for Rh sensitization is of course the *in vivo* one. Wiener's biological test<sup>28</sup> will be found useful when there is neither time nor facilities for performing Rh tests, and has the advantage that it will also detect sensitization to other blood factors as well. Fifty c.c. of the prospective donor's citrated blood is injected intravenously by syringe, or diluted in saline and given by the gravity method. A sample of the patient's plasma taken 60 to 90 minutes after the injection is compared with a sample of pretransfusion plasma, and if it is not appreciably darker, any amount of blood from the same donor may be given without danger. In positive

\*\*It is remarkable that these irregular agglutinins all reacted best at low temperature. In almost all of the subsequent cases, the agglutinins, when detectable at all, reacted best at body temperature. This apparent paradox has been explained by the recent discovery of the Rh blocking antibodies<sup>37, 38</sup>, which were present in the sera of the patients studied by Wiener and Peters. According to Wiener, in tests at body temperature, the blocking antibodies rapidly combined with the test Rh-positive cells and prevented the action of the Rh agglutinins also present in the patients' sera. In tests at refrigerator temperature, the blocking antibodies reacted more slowly so that the Rh agglutinins were able to clump the test cells.

reactions, the patient not infrequently has a chill and rise in temperature 50 to 60 minutes after the injection; however, the clinical symptoms are inconsistent and may be mild or absent. In any event, an appreciable increase in the icteric index, e.g., from 3 to 5, is evidence of hemolysis and another donor should be tried.

(4) In analyzing their cases of intragroup hemolytic transfusion reactions, as well as others reported in the literature, Wiener and Peters<sup>26</sup> found that these fall into two well-defined groups: (a) patients receiving repeated transfusions, as already discussed; and (b) patients never previously transfused. In the cases of intragroup hemolytic reactions following an initial transfusion it was invariably found that the patients were females, either pregnant at the time or having had a previous pregnancy. This indicated a second mechanism by which an Rh-negative patient could become sensitive to the Rh factor; namely, by isoimmunization in pregnancy, a phenomenon that had previously been mentioned by Levine and Stetson<sup>12</sup> to explain an intragroup hemolytic reaction observed by them. Since, as Landsteiner and Wiener<sup>11</sup> have shown, the Rh factor is inherited as a simple Mendelian dominant, an Rh-negative woman wedded to an Rh-positive man can have Rh-positive children.\* If, during the pregnancy, some of the fetal Rh-positive blood gains access to the maternal circulation, and the woman becomes sensitized in this manner, a subsequent initial transfusion of Rh-positive blood could give rise to a severe hemolytic reaction.

Pursuing the study of isoimmunization in pregnancy further, Levine and his associates discovered another clinical application of the Rh factor, namely, its role in erythroblastosis fetalis.<sup>15</sup> Through the work of Diamond, Blackfan and Baty<sup>6</sup>, this disease had been shown to include the syndromes of hemolytic anemia of the newborn, icterus gravis, and hydrops fetalis, as well as certain hitherto obscure stillbirths. As early as 1923, Ottenberg<sup>22</sup> attempted to establish a relationship between heterospecific pregnancy (incompatibility between the blood groups of fetus and mother) and icterus gravis neonatorum, but this hypothesis proved to be incorrect. In 1938, Darrow<sup>5</sup>, for the first time, put forward the theory of isoimmunization in pregnancy to account for this disease, but the Rh factor had not yet been discovered, and she incorrectly assumed that fetal hemoglobin was the antigen at fault. When Levine and his associates<sup>3,13</sup> noticed that women who have had pregnancy complications, in particular, stillbirths or infants with erythroblastosis, were also subject to intragroup hemolytic transfusion reactions, the idea occurred to them that the Rh factor might be responsible.

According to the theory of Levine et al.<sup>16</sup>, certain Rh-negative women bearing Rh-positive infants become isoimmunized (or sensitized), and the Rh isoantibodies which they produce then filter through the placenta into the fetus and destroy its erythrocytes, giving rise to one or another manifestation of the disease.

This theory was soon shown to be correct when Levine et al.<sup>14</sup>, found that, among mothers of erythroblastotic infants, as many as 90 per cent are Rh negative, in contrast to the incidence of only 15 per cent Rh-negative individuals (male or female) in the general population. In addition, whenever the mother was Rh negative, the father and child were Rh positive. Moreover, in about half the cases Rh isoagglutinins could be demonstrated in the maternal serum, proving that she was sensitized to the Rh factor. These observations were quickly corroborated by other workers<sup>23,29</sup>, and British investigators<sup>1</sup> reported a much higher percentage of mothers with demonstrable isoagglutinins. In view of the now well-established pathogenesis of the disease, it has been recommended that the name "erythroblastosis" be discarded, and the term "hemolytic disease of the fetus and newborn" substituted. This suggestion

\*If the husband is homozygous (genotype  $RhRh$ ) all the children will be Rh positive; if the husband is heterozygous (genotype  $Rhrh$ ) half of the children will be Rh positive and half Rh negative. When the husband and wife are both Rh negative (genotype  $rhrh$ ), obviously all the children will be Rh negative. If both parents are Rh positive, all the children will be Rh positive except when the two parents are heterozygous, in which event  $\frac{3}{4}$  of the children will be Rh positive and  $\frac{1}{4}$  negative.

has been generally adopted, because erythroblastosis is not a consistent feature of the disease, while hemolysis is.

One puzzling observation was the lack of correlation between the anti-Rh agglutinin titer in the maternal serum and the severity of disease in the infant. In some of the most severe cases, anti-Rh isoagglutinins were not detectable in the maternal serum, while at least one case has been reported in which a woman with high-titered Rh isoagglutinins gave birth to an apparently normal infant.<sup>7</sup> These apparent paradoxes have been solved, at least in part, by the discovery of the Rh-blocking isoantibodies referred to above.

Another problem was raised by the fact that families with Rh-negative mothers and Rh-positive fathers and infants occur with a frequency of about 9 or 10 per cent, while hemolytic disease occurs only in one out of 250 to 500 births. Some workers have attributed this to differences in permeability of the placenta to the fetal erythrocytes, but a more reasonable explanation appears to be the differences in the capacity of the mothers to become sensitized. As was already pointed out, only one in 25 to 50 Rh-negative individuals is readily sensitized by transfusions of Rh-positive blood, and the same appears to hold in the case of sensitization by pregnancy. With regard to the exceptional 10 per cent of cases of hemolytic disease in which the mother is Rh positive, these have been largely explained by the discovery of the eight Rh blood types, and the Hr factor, while rare cases appear to be due to isoimmunization against the common blood group factors A, B and O, and possibly even M and P.

The discovery of the role of the Rh factor in hemolytic disease of the fetus and newborn, has resulted in a more rational transfusion therapy of infants suffering from the disease. The use of Rh-negative, instead of Rh-positive blood, has reduced the number of transfusions required to effect a cure, and has saved the lives of the babies who would have succumbed under the older method of treatment.<sup>9,17,20,32</sup> Infants with hemolytic disease should not be allowed to nurse because Rh isoantibodies may be present in colostrum and milk.

While most of the earlier studies on the Rh factor were carried out with anti-rhesus immune animal sera,\* in recent years the tendency has been to employ human sera obtained from Rh-negative mothers of erythroblastotic infants. While only a small percentage of such mothers yield usable antisera, the best human sera give stronger reactions and are easier to work with than the best animal sera. As Fisk and Foord<sup>8</sup> have shown, the antirhesus sera also have the peculiarity that they strongly agglutinate the blood cells of fetuses and newborn, whether Rh positive or Rh negative, and are therefore not satisfactory for testing such blood. The antirhesus sera have the advantage that they all give parallel reactions, identical with original sera of Landsteiner and Wiener, and therefore can be used as standard. The human sera differ in specificity and therefore cannot be used until they have been standardized. This phase of the subject has been clarified by the work of Wiener and his associates<sup>31,33,36,38</sup> on the eight Rh blood types, their serology, heredity and nomenclature.

The most common human anti-Rh agglutinin gives reactions parallel with the standard anti-rhesus agglutinin, and is designated as anti-Rh<sub>0</sub>. Two other varieties of human anti-Rh agglutinins have been found; one gives about 70 per cent positive reactions with the blood from white individuals and is designated as anti-Rh' (Wiener<sup>27</sup>), the other gives about 30 per cent positive reactions and is designated as anti-Rh'' (Wiener and Sonn<sup>34</sup>). With the aid of these three varieties of Rh isoagglutinins, eight types of human blood can be differentiated as shown in Table I. Because of the special position of the factor detected by anti-Rh<sub>0</sub> sera, the eight types fall into

\*Sera prepared in guinea pigs proved to give more satisfactory reactions than the original antisera prepared in rabbits. A highly satisfactory antirhesus serum has been prepared by Dr. A. F. Coca in other animals.

# PROGRESS IN ALLERGY

TABLE I. CLASSIFICATION OF THE RH BLOOD TYPES  
(Wiener<sup>33</sup>)

Bloods lacking Rh <sub>0</sub>				Bloods containing Rh <sub>0</sub>			
Designations of types	Reactions with antisera			Designations of types	Reactions with antisera		
	Rh'	Rh''	Rh <sub>0</sub>		Rh'	Rh''	Rh <sub>0</sub>
Rh neg.	—	—	—	Rh <sub>0</sub>	—	—	+
Rh'	+	—	—	Rh <sub>1</sub> (Rh' <sub>0</sub> )	+	—	+
Rh''	—	+	—	Rh <sub>2</sub> (Rh'' <sub>0</sub> )	—	+	+
Rh'Rh''	+	+	—	Rh <sub>1</sub> Rh <sub>2</sub>	+	+	+

TABLE II. THE SIX STANDARD RH GENES AND THE REACTIONS WHICH THEY DETERMINE  
(Wiener et al.<sup>39</sup>)

Designation of genes	Reactions of agglutinogens with antisera			
	Rh'	Rh''	Rh <sub>0</sub>	Hr
<i>rh</i>	—	—	—	+
<i>Rh<sub>0</sub></i>	—	—	+	+
<i>Rh'</i>	+	—	—	—
<i>Rh<sub>1</sub></i>	+	—	+	—
<i>Rh''</i>	—	+	—	+
<i>Rh<sub>2</sub></i>	—	+	+	+

four natural pairs, giving rise to what amounts to a double scheme of four types each, analogous serologically and genetically to the four common blood groups. (Incidentally, this considerably simplifies the task of learning and remembering the scheme of the Rh blood types.) In general, the types are named after the antisera with which they react. Blood reacting with anti-Rh<sub>0</sub> and anti-Rh' are designated Rh<sub>0</sub>' or more simply and preferably Rh<sub>1</sub>, instead of Rh<sub>0</sub>Rh', because genetic studies have shown this property to be due as a rule to the action of a single gene *Rh<sub>1</sub>* which produces a single agglutinin, but reacts with two antisera just as *A<sub>1</sub>* blood reacts with both  $\alpha_1$  and common  $\alpha$  agglutinins. This same explanation applies for the designation of type Rh<sub>2</sub>. Types Rh'Rh'' and Rh<sub>1</sub>Rh<sub>2</sub>, on the other hand, are so named because they result from the combination of a pair of allelic genes (cf. Table III).

Of the three factors, Rh<sub>0</sub> is by far the most antigenic, Rh' is less antigenic, while Rh'' is the least antigenic. Individuals of types Rh', Rh'' and Rh negative are therefore most apt to have intragroup hemolytic transfusion reactions and erythroblastotic infants. Type Rh<sub>1</sub> individuals may rarely become sensitized to the Rh'' factor in bloods of types Rh<sub>2</sub> and Rh<sub>1</sub>Rh<sub>2</sub>, while type Rh<sub>2</sub> individuals have rarely become sensitized to the factor Rh' in bloods of types Rh<sub>1</sub> and Rh<sub>1</sub>Rh<sub>2</sub>, thus accounting for some instances of Rh sensitization in Rh-positive individuals. Obviously, such patients may be transfused either with blood of their own Rh type or Rh-negative blood, because Rh-negative individuals hold the same position in the scheme of the Rh blood types as group O individuals in the scheme of the four common blood groups.<sup>35</sup>

An important cause of intragroup sensitization in Rh-positive individuals is the Hr factor. This property was first described by Levine and Javert,<sup>18</sup> who detected

# PROGRESS IN ALLERGY

TABLE III. THE EIGHT RH BLOOD TYPES, THEIR DISTRIBUTION AND THE RELATION TO THEM OF THE HR FACTOR  
(Wiener et al.<sup>39</sup>)

Rh blood types	Distribution among (per cent)		Reactions with antisera			Genotypes	Reactions with anti-Hr serum
	Whites	Negroes	Rh'	Rh''	Rh <sub>0</sub>		
Neg.	12.9	8.1	Neg.	Neg.	Neg.	<i>rrh</i>	Strong
Rh <sub>1</sub>	54.1	20.2	Pos.	Neg.	Pos.	$\left\{ \begin{array}{l} Rh_1 Rh_1 \\ Rh_1 Rh' \\ Rh_1 rh \\ Rh_1 Rh_0 \\ Rh' Rh_0 \end{array} \right\}$	$\left. \begin{array}{l} \text{Neg.} \\ \text{Weak} \end{array} \right\}$
Rh <sub>2</sub>	16.0	22.4	Neg.	Pos.	Pos.	$\left\{ \begin{array}{l} Rh_2 Rh_2 \\ Rh_2 Rh'' \\ Rh_2 rh \\ Rh_2 Rh_0 \\ Rh'' Rh_0 \end{array} \right\}$	$\left. \begin{array}{l} \text{Strong} \end{array} \right\}$
Rh <sub>1</sub> Rh <sub>2</sub>	13.2	5.4	Pos.	Pos.	Pos.	$\left\{ \begin{array}{l} Rh_1 Rh_2 \\ Rh_1 Rh'' \\ Rh' Rh_2 \end{array} \right\}$	$\left. \begin{array}{l} \text{Weak} \end{array} \right\}$
Rh <sub>0</sub>	2.6	41.2	Neg.	Neg.	Pos.	$\left\{ \begin{array}{l} Rh_0 Rh_0 \\ Rh rh_0 \end{array} \right\}$	$\left. \begin{array}{l} \text{Strong} \end{array} \right\}$
Rh'	0.9	2.7	Pos.	Neg.	Neg.	$\left\{ \begin{array}{l} Rh' Rh' \\ Rh' rh \end{array} \right\}$	$\left. \begin{array}{l} \text{Neg.} \\ \text{Weak} \end{array} \right\}$
Rh''	0.3	—	Neg.	Pos.	Neg.	$\left\{ \begin{array}{l} Rh'' Rh'' \\ Rh'' rh \end{array} \right\}$	$\left. \begin{array}{l} \text{Strong} \end{array} \right\}$
Rh' Rh''	0.01	—	Pos.	Pos.	Neg.	<i>Rh' Rh''</i>	Weak

in the serum of an Rh-positive mother of an erythroblastotic infant an agglutinin which acted on all Rh-negative bloods and all Rh-positive bloods which did not react with anti-Rh' serum. Because the property is present in all Rh-negative bloods it was designated Hr (the opposite of Rh). The nature of the Hr factor has been clarified by the work of Race and Taylor<sup>24</sup> who showed that it was present in the agglutinogens determined by genes *rh*, *Rh<sub>0</sub>*, *Rh<sub>2</sub>* and *Rh''*, but absent from the agglutinogens determined by genes *Rh<sub>1</sub>* and *Rh'* (cf. Table II). Race and Taylor's theory has recently been corroborated by statistical studies of Wiener et al.<sup>39</sup>, and the implications of the theory are summarized in Table III taken from the paper of Wiener et al. In cases of erythroblastosis due to Hr sensitization, the mother is Hr negative, and the father and child Hr positive. Hence, the mother must belong to type Rh<sub>1</sub> (genotype *Rh<sub>1</sub> Rh<sub>1</sub>* or, rarely, genotype *Rh<sub>1</sub> Rh'*) or extremely rarely to type Rh' (genotype *Rh' Rh'*). Despite statements to the contrary<sup>19</sup>, the child can never be Rh negative (or belong to types Rh<sub>2</sub>, Rh<sub>0</sub> or Rh''), because it must inherit one *Rh<sub>1</sub>* or *Rh'* gene from the mother. There is no restriction as to the type of the father because Hr-positive individuals may occur in all eight Rh blood types.<sup>39</sup>

Obviously, an up-to-date blood donor service will eventually have to include a panel of Hr-negative donors as well as Rh-negative donors. Before transfusing sensitized Rh-positive individuals who belong to type Rh<sub>1</sub>, a biological test with Hr-

negative blood should be tried. The same procedure may be followed when transfusing erythroblastotic babies with Rh-positive mothers of type Rh<sub>1</sub>. The simplest and safest method of treating erythroblastotic infants with Rh-positive mothers, however, is to transfuse the mother's washed erythrocytes suspended in saline or compatible plasma, provided the mother is well enough to act as donor.

It is evident that the discovery of the Rh factor has supplied the key to an intricate field of considerable clinical importance. There is no doubt that there is still much of fundamental importance to be learned concerning this intriguing subject.

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Regents,

## Histamine

*Histamine Tolerance.* Katzenstein, R.: *Yale J. Biol. & Med.*, 16:325, 1944.

By the daily repeated intravenous injection of increasing quantities of histamine, tolerance to the drug can be developed. The author demonstrates this in describing his work with dogs. Increased tolerance to histamine for the dog is not associated with adrenal cortical hypertrophy. Nontolerant controls show lesions of the central nervous system, gastro-intestinal tract and spleen. These are believed due to the acute hypotension and the inefficiency of the circulating blood volume.

# News Items

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Recently, Dr. Irving W. Schiller, Boston, a Fellow of the College, presented the Research Fund with contributions from grateful patients—Mr. A. J. Rahnovitz, Mr. Nathan H. Friedman and Miss M. Karas.

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At the May meeting of the Pittsburgh Allergy Society, the following scientific program was presented: "Lens Protein Sensitization," Dr. A. R. McCormick; "Contact Dermatitis," Dr. A. Harvey Neidorff; group discussion of "High or Low Dosage Therapy in Inhalant Allergy," led by Dr. John E. Gordon.

Dr. James A. Mansmann, a Fellow of the College, is secretary of the Society.

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Dr. Leon Bentolila of Buenos Aires, Argentina, and Dr. Arturo Mardones, Santiago, Chile, Fellows of the College, who were engaged in postgraduate studies at Doctor Rowe's clinic at Oakland and San Francisco, have returned to their native countries to resume their practice of allergy.

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Dr. Ulysses Fabiano Alves, Jr., Rio de Janeiro, an Associate Fellow of the College, who has completed studies at the Mayo Clinic and New York Hospital, is at the present time doing special work in allergy at the Vaughn Memorial Clinic under the direction of Dr. J. Warrick Thomas.

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Professor E. C. Stakman, an Honorary Fellow of the College, and Chief of the Division of Plant Pathology and Botany of the Department of Agriculture at the University of Minnesota, has returned from Mexico City where he has been making special studies in plant pathology. On his return, he made rust surveys throughout the central portion of the United States.

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Dr. Frank G. Crandall, an Honorary Fellow of the College, has been discharged from the Army and has established offices at Los Angeles, California, in the Wilshire Professional Building, 3875 Wilshire Boulevard. His practice will be limited to allergy. For three years Doctor Crandall served on active duty in the Pacific area as Colonel in the Medical Corps.

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The University of Illinois College of Medicine announces its sixth semi-annual Refresher Course in Laryngology, Rhinology and Otolaryngology, September 24 through September 29, 1945, at the College, in Chicago. The course is intensive and largely didactic, but some clinical instruction is also provided.

It is especially suited to specialists unable to devote a longer period for advanced instruction and to others seeking a comprehensive review of the field of otorhinolaryngology. The number of registrants will be limited. It is therefore desirable to apply for registration immediately. The fee is \$50. Write to Dr. A. R. Hollender, Chairman, Refresher Course Committee, Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

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The College gratefully acknowledges the second gift of \$300 made by the Allergen-Proof Encasings, Inc., Cleveland, Ohio, for purposes of scientific research and investigation in the field of allergy.

This fund will be applied towards the College fellowships now established at the Mayo Foundation and in the Department of Biochemistry of the University of Cincinnati.

A grant of \$200 has been made by the Hollister-Stier Laboratories, makers of allergens, to The Committee of Allergists for the Study of the Unknown Causes of Hay Fever. This sum is to be used for research purposes by the Committee as it sees fit when attempting to solve what is commonly known in the South as the "X hay fever" problem.

A history and description of the condition, as well as the areas involved, are very adequately discussed in Wodehouse's recent book "Hayfever Plants," *Chronica Botanica*, Waltham, Massachusetts, 1945.

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Almay, Incorporated, manufacturers of hypo-allergenic cosmetics, has contributed to the Educational Committee of the American College of Allergists a fund of \$500 for the year 1945, to be used by the Committee for undergraduate teaching, as it sees fit. The Committee and the Board of Regents, when accepting this contribution, acknowledge their gratitude for this generous grant. The Committee will use this fund for undergraduate teaching in allergy where it considers it will do the most good.

## COLLEGE RESEARCH FOUNDATION

In the November-December, 1943, issue of the *ANNALS OF ALLERGY* an announcement was made of the establishment of a College Research Foundation, since it was thought best to have the College members initiate the first fund to be used for research in allergy. A plea was made that 100 Fellows of the College, who are able and willing to do so, contribute \$50 each towards the Fund, such contributors to constitute an honor roll. Although the amount of \$50 was an arbitrary sum, some contributed more and others less towards this Fund. At that time it was also stated that personal solicitation would be avoided as much as possible. There was a very ready response at the beginning, but since no more notice has been given to this Fund and several hundred more members have been taken into the College, we think that it is fitting to announce the names of those who have made such contributions. Some of the members generously responded with more than double the amount requested. These were some of the instructors who participated in the instructional course at St. Louis and who turned over the amount of their expenses to the College.

With considerable funds still needed for the Fellowships established at the Mayo Foundation and the University of Cincinnati, we are appealing to those members of the College, who are able to do so, to send in their contributions. These funds are deposited in a separate account of the College and will be used in payment of the two fellowships that have been established or for other research, and then only upon the direction of the members of the Board of Regents and the President of the College.

Incidentally, an audit of all funds of the College is presented to the Board of Regents at each of its meetings. Every member in the College has received a statement of the financial condition of the College as of September 30, 1944 (prepared by a certified public accountant), and will receive the same this year.

Those who have contributed to this College Research Foundation are: Dr. W. Byron Black, Kansas City, Mo., Dr. Ralph Bowen, Houston, Texas, Dr. Norman W. Clein, Seattle, Wash., Dr. John P. Henry, Memphis, Tenn., Dr. Florence M. Kline, Pittsburgh, Pa., Dr. Delbert J. Parsons, Springfield, Ohio, Dr. Homer E. Prince, Houston, Texas, Dr. Harry L. Rogers, Philadelphia, Pa., Dr. Ralph H. Spangler, Philadelphia, Pa., Dr. Orval R. Withers, Kansas City, Mo., Dr. Fred W. Wittich, Minneapolis, Minn. This list does not include the generous donations already made by commercial groups and other friends of the College, which have already been announced in these columns.



## NEWS ITEMS

Dr. G. Estrada de la Riva of Havana, Cuba, an Active Fellow of the College and editor of the Spanish supplement, published by the College, has been appointed Professor in Allergy for an extension course to be presented at the University of Havana this summer. Although these postgraduate courses have been held the past four years, this is the first time that allergy has been given consideration enough to be included. Doctor de la Riva is Associate Professor of Experimental Pathology at the University.

### ANNOUNCEMENT

At the recent meeting of the Board of Regents, held at Cleveland June 2 and 3, it was decided that the Questions and Answers department of the ANNALS be resumed since there have been many requests that it appear. Members are urged to submit any questions which may arise in their practice of allergy, which will be referred to the best known authorities for reply in the ANNALS. It is not necessary that the queries be signed other than "M.D." and the name of the state mentioned.

The New and Unused Therapeutics Committee of the College is now functioning. Dr. Ethan Allan Brown is Chairman of this committee, and Drs. Philip M. Gottlieb, George E. Rockwell, Frank A. Simon and Erich Urbach have been appointed to serve on the same. It was decided that a page headed "New and Unused Drugs" be included in the ANNALS, in which articles will be published which will be signed by the member of the committee making the report or by the Chairman of the committee. The literature concerning important drugs will be reviewed and the drugs given a trial, when feasible. Members are asked to submit questions concerning drugs. Certain preparations about which there has been some controversy will be investigated.

### INSTRUCTIONAL COURSES AVAILABLE

Sets of the complete intensive instructional courses covering all phases of important allergic diseases, presented at St. Louis, November 4 to 8, inclusive, are still available. They include comprehensive outlines and lectures including tables, figures, diets, prescriptions, etc., with space for additional notes.

Subjects and authors are listed below:

- Dermatologic Allergy—Rudolf L. Baer, M.D., New York, N. Y.
- The Physiologic and Immunologic Aspects of Allergy (Illus.)—F. W. Wittich, M.D., Minneapolis, Minn.
- The Diagnosis and Treatment of Allergy of the Nose and Paranasal Sinuses—French K. Hansel, M.D., St. Louis, Mo.
- Some Neurologic and Psychologic Aspects of Allergy—Michael Zeller, M.D., Chicago, Ill.
- Food and Digestive Allergy (Illus.)—Herbert J. Rinkel, M.D., Kansas City, Mo.
- Allergy of the Central Nervous System—T. Wood Clarke, M.D., Utica, N. Y.
- Drug Allergy—Jonathan Forman, M.D., Columbus, Ohio.
- Pediatric Allergy—Ralph Bowen, M.D., Houston, Texas.
- Allergy Elimination Diets for Children, Albert V. Stoesser, M.D., Minneapolis, Minn.
- Mold Allergy (Illus.)—Homer E. Prince, M.D., Houston, Texas.
- Bronchial Asthma—Leon Unger, M.D., Chicago, Ill.
- Physical Allergy—Cecil M. Kohn, M.D., Kansas City, Mo.

The price of the complete set is \$3. Please mail your check with your order.

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# BOOK REVIEWS

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THE SPECIFICITY OF SEROLOGICAL REACTIONS. By Karl Landsteiner, M.D., The Rockefeller Institute for Medical Research, New York. Price, \$5.00. Cambridge, Mass.; Harvard University Press, 1945.

Landsteiner succeeded in finishing all but the final writing of the revision of his opus magnum before final illness put an end to his labors. Thus, the man who, more than anyone else, contributed to make immunology an integrated part of science, leaves us, like a testament, his views on the status of immunology and the avenues of further progress. Landsteiner presents in Brueghelian detail all the infinitely varying aspects of the subject. The book is replete with references to the original papers or, where such references became too numerous, with quotations of reviews or other publications where details on literature can be found. The mellowness of viewpoint and richness in detail makes this book an invaluable companion for the immunologist. It is, however, no longer—as were the previous editions—a book the beginner will enjoy reading as an introduction to immunology.

The chapters on chemospecificity and on supersensitivity to simple substances are of particular importance to those who are interested in the basic aspects of allergy. They provide a most valuable guidance to the critical appraisal of experimentation in our field. Not every allergist will agree with Landsteiner's viewpoints on the interrelations of allergic phenomena and anaphylaxis, but that will not impede the profit the reader will derive from the example of a sober and thorough analysis of factual knowledge at hand. With Landsteiner, we lost one of the very few who are able to unite in one person the chemical, immunological and medical experience which alone will guide us safely through the confusing perplexity of our problems. The progress in our field will depend more and more on the co-operation of the chemical and the immunological technologist with the clinician. For those who strive for the integration of experimental and clinical observation, Landsteiner's book will remain a spiritual guide for a long time to come.

A. J. WEIL.

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PRINCIPLES AND PRACTICES OF INHALATIONAL THERAPY. By Alvan L. Barach, M.D., Associate Professor of Clinical Medicine, Columbia College of Physicians and Surgeons; Assistant Attending Physician, Presbyterian Hospital. 315 pages. 51 illustrations. Price \$4.00. Philadelphia: J. B. Lippincott Company, 1944.

This book is intended as a guide to physicians responsible for the technical procedures used in inhalational therapy and those who wish to understand the physiologic basis for the same. The author, a pioneer in developing the practice of inhalational therapy, has compiled in a clear and concise manner a handbook on the methods of inhalational therapy in considerable detail. The importance of inhalational therapy is becoming widespread. Modern medical practice is applying it in heart failure, coronary artery disease, postoperative atelectasis, new born atelectasis, pneumonia, pulmonary edema, emphysema, bronchial asthma, cerebral thrombosis and pulmonary infarct, as well as the treatment of war gas poisoning severe hemorrhage, altitude sickness and shock.

The pathologic physiology of respiration of the various clinical entities considered determines both the specific indication for treatment, as well as the selection of the method of inhalational therapy. These methods, are briefly but clearly de-

tailed so that the physician may be guided to the selection of the proper apparatus and the employment of the most efficient method when carrying out this form of therapy. Technicians and nurses who carry out the detailed procedures of inhalant therapy may also find the clinical factors in the book very valuable.

Each chapter is followed with an adequate essential bibliography. There are thirty-eight chapters beginning with the historic and physiologic background of inhalational therapy and including the therapeutic use of oxygen, carbon dioxide, helium, and the use of positive pressure and vaporized solutions of epinephrine and neosynephrin. The second chapter defines and presents the causes, as well as the pathologic physiology, symptoms and inhalational therapy of acute altitude sickness and acute anoxia. The treatment of pneumonia, coronary thrombosis and coronary sclerosis, shock, pulmonary infarction, massive collapse, postoperative atelectasis are clearly presented in succeeding chapters.

Chapter 11 on "Bronchial Asthma" is of particular value to allergists. The disease in relation to inhalational therapy is clearly defined. The pathologic physiology with particular reference to the physical advantage of helium-oxygen mixture over air is given in detail, with studies in vital capacity, as well as the use of aminophyllin therapy in conjunction with helium-oxygen inhalation in patients with intractable asthma which is of extreme practical value to any physician in treating acute asthma.

In order to appreciate the number of diseases benefited by inhalational therapy the following conditions are enumerated which are adequately discussed: obstructive lesions in the respiratory tract, pulmonary emphysema, accidental asphyxia, hemorrhage, peripheral arteriosclerosis, migraine, seasickness, gas gangrene, tetanus, anesthesia, anoxia and brain lesions following fever therapy, head injuries, paralysis of the respiratory musculature, cerebral embolism and thrombosis, chronic pulmonary tuberculosis, blast injuries of the lungs, aerial transportation of diseased patients, oxygen poisoning and submarine medicine and caisson disease.

The final chapters are given over to the methods of inhalational therapy with the illustrations of mechanical devices used, detailed procedures, et cetera, with the various diseases mentioned.

This book is the last word in the therapeutic uses of gases and clinical medicine, and no doctor in private practice or member of a hospital staff should be without it.

F.W.W.

## Experimental Approach to Oral Treatment of Food Allergy

(Continued from Page 186)

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## THE EFFECT OF GLUTAMIC ACID ON THE HYDROGEN ION CONCENTRATION (pH) OF THE URINE IN PETIT MAL TYPES OF EPILEPSY

A Daily Record for One Year of the Urinary pH of an Epileptic Patient  
with an Allergic Background, to Whom Four Forms of Glutamic  
Acid Were Administered in Various Daily Amounts

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A MODIFICATION in the severity and frequency of petit mal types of epilepsy has been found possible through increasing the hydrogen ion concentration of the urine to a pH of 5, 4 or lower by the daily administration of glutamic acid in various forms and amounts.

This biochemical metabolic modification (soil alteration), has been reported of benefit in allergic patients recently by Forman<sup>5</sup> who states he "has been accustomed for a number of years to use glutamic acid hydrochloride in 5-grain capsules, after meals, because of low gastric acidity in allergic individuals."

Bookhammer<sup>1</sup> in a recent lecture at a seminar on Mental Hygiene, under the auspices of the Philadelphia County Medical Society, stated that he had obtained improvement in patients with epileptic seizures by the use of a teaspoonful of glutamic acid added to a glass of milk, taken three times daily after meals. He reported, however, considerable difficulty in securing the material.

In August, 1943, Price, Waelsch and Putnam<sup>10</sup> were the first to report "On the Use of dl-Glutamic Acid Hydrochloride in Treatment of Petit Mal and Psychomotor Seizures." They stated that grand mal seizures were unaffected by the administration of the glutamic acid. The encouraging results, reported by the addition to known anticonvulsive therapy, of glutamic acid is recorded by them in a summarized detail of eight patients, in all of whom the minor seizures were benefited.

In reporting<sup>12,13</sup> two series of epileptic patients, totaling 305 cases, I found some form of allergy present in over fifty per cent, and in the an-

cestors of these 305 patients there occurred 517 instances of allergy in one form or another (asthma, hay fever, urticaria, eczema, migraine) or a demonstrable gastrointestinal disturbance of probable allergic origin.

As a metabolic alterative, I have used for over thirty-five years, the intramuscular injection of a solution of venom protein (crotalin) in most of the more than 1,000 epileptic patients I have studied and treated since 1909.<sup>14</sup> The mechanism of the action of crotalin has been shown to include its eosinophilogenic properties<sup>15</sup>, its plasma activating influence<sup>17</sup>, its ability to increase cell permeability<sup>4,7,11,16</sup>, its action in causing peripheral vascular dilatation<sup>4</sup>, its altering influence on enzymes<sup>9</sup> and colloids<sup>6</sup> together with other modifications of metabolism.

#### PRESENT CLINICAL INVESTIGATION

During the past eighteen months, in the treatment of six patients who were subject to both grand and petit mal types of epileptic seizures, I have added one or another form of glutamic acid to their other medications. These patients were selected because all previous therapy had had little or no effect on their petit mal seizures. All six patients had been receiving dilantin sodium either alone or in combination with phenobarbital before coming under my care, and the intervals of their convulsive seizures had been variously lessened in frequency or modified in severity, but the petit mal manifestations were little or not at all affected.

The anticonvulsive sedative therapy was continued while I treated these patients, and, in addition, they were given, every seven to fourteen days, an intramuscular injection of crotalin, the strength dose of which was guided by the percentage of eosinophils<sup>15</sup> in the differential blood counts made just before and twenty-four hours after an injection. The dose of crotalin ranged from 1/400 to 1/50 of a grain.

Glutamic acid was then added to the crotalin-dilantin-phenobarbital therapy, with a noticeable reduction in frequency, and modification in the character and severity of the petit mal seizures. The effect, to a greater or less degree, was practically the same in all six patients. Accordingly, the data from one patient only is reported in detail as an illustration. All six patients used a diet with a preponderance of protein, i.e., food with acid ash, in the proportion of two to three parts to one part alkaline ash base, as originally suggested by MacQuarrie.<sup>8</sup> No special article or type of food was excluded, unless there was a natural antipathy of the patient to a given food or a definite allergic response was shown to certain foods by skin testing.

#### FORMS OF GLUTAMIC ACID USED

Three forms of Glutamic Acid (Lederle) were used, i.e., *dl*-Glutamic Acid Hydrochloride in 0.5 gm. capsules; *d*-Glutamic Acid Hydrochloride in 0.58 gm. capsules, and Glutamic Acid Hydrochloride in 0.324 capsules (the latter stocked as "Glutan," H-C-L). All were furnished through the courtesy of Benjamin W. Carey, M.D., Director of Lederle Labora-

tories. Natural dextrorotatory Glutamic Acid (Parke, Davis & Co.) in 0.5 gm. tablets were also used at times in clinical comparison. The latter form of Glutamic Acid, i.e., the natural dextrorotatory, has been designated in a second paper by Waelsch and Price<sup>17</sup>, with a nomenclature of *l* (+) Glutamic Acid, which they report of as much clinical value as the *dl*-Glutamic Acid Hydrochloride.

#### CASE HISTORY AND MEDICATION

The data of the clinical investigation reviewed in detail in this case includes: the patient's and her families' history; the anticonvulsant and metabolic alternative medication used; the various size doses and forms of Glutamic Acid administered, together with the daily record, for one year, of the patient's urinary pH.

The patient, at the age of thirty-three years, has been married for seven years. She is a college graduate, has done some high school teaching and her own housework since marriage.

She was a first-born, full-term baby, instrumentally delivered, breast-fed for a few months but owing to "bilious attacks" did not gain so the diet was changed to condensed milk, and thereafter there were fewer and modified gastrointestinal upsets. No specific food sensitivity could be determined. No spasms occurred in infancy, she had measles at third year, chicken pox at fifth year and whooping cough after starting school. She was subject to "strawberry rash" as a child, and after adolescence, to ivy poisoning. Milk and cream have always, since childhood, caused "gastrointestinal upsets." There is also an antipathy to butter. Skin tests, however, were negative to milk, egg and wheat. Menstruation was established at thirteen year, has always been of 28-day type, and without cramps. No accidents or injuries have ever occurred causing unconsciousness.

*Seizure History.*—Petit mal started at seventh year and continued at irregular intervals of a few days to a week with an occasional longer interval. The first convulsion occurred at the time the menarche was established in her thirteenth year. The major type of seizure recurred thereafter at intervals of one to three months; petit mal occurring between the convulsive attacks at intervals of from one to three to seven days and occasionally, three, four or five in the same day, but always more likely to occur during or just after a menstrual period. Many of the lighter forms of momentary lapses were referred to by the patient and her family as "haziness." They did not interfere with the patient completing a college course, teaching school for a time and marrying in her twenty-third year. At her twenty-fifth year a three months' pregnancy increased both types of seizures, and was terminated at the third month, but both forms of attacks continued to recur at about the same frequency as they did prior to the pregnancy.

*Family Allergic History.*—The father is subject to neuralgic headaches, ivy poison and urticaria, which has occurred repeatedly following honey sensitivity. Her mother had "uremic" convulsions at the patient's birth, and has been subject to urticaria all her life. Mother's brother, now forty years of age, is subject to convulsive seizures. Maternal grandmother suffered from periodic headaches with vomiting (allergic migraine).

*Treatment and Its Effect on Seizures.*—Anticonvulsant therapy began with phenobarbital, started after the first grand mal seizure in 1924 and was continued until September, 1940. During the period of report, now available, beginning with Jan-

TABLE I. URINARY pH AND RECORD OF SEIZURES

November 20, 1943–March 13, 1944

Date 1943	1st A.M. or other hour specimen  Urinary pH	Total Amount Taken Daily in 3 Doses, after Meals.† Gms.	Record of Seizures and Comment
Nov. 20	A.M. 4	3.0	<i>dl</i> -Glutamic Acid Hydrochloride (in capsules)
21	" 7*	4.5	*—30 grs. Sod. Bicarb.—Indigestion.
22	" 5	1.5	
23	" 5	1.5	
24	" 4	1.5	
25	" 6	3.0	
26	" 4	1.5	
27	" 5	1.5	
28	" 4	3.0	
29	" 4	1.5	
30	" 4	1.5	
Dec. 1	" 4	1.5	
2	" 4	1.5	
3	" 5	1.5	
4	" 5	1.5	
5	" 6	4.0	●●—during the day
6	" 4	3.0	●●●—during the day
7	" 4	1.5	
8	" 4	1.5	
9	" 4	1.5	
10	" 4	1.5	
11	" 5	1.5	
12	" 5	1.5	Menstruation—(Dec. 12 to 15)
13	" 5	1.5	
14	" 4	1.5	
15	" 5	1.5	
16	" 4	1.5	
17	" 5	1.5	
18	" 4	1.5	
19	" 6	2.0	
20	" 4	1.5	
21	" 4	1.5	
22	" 4	1.5	●—9 A.M.
23	" 4	1.5	●—10 P.M.
24	" 4	1.5	●—1 P.M.
25	" 4	1.5	
26	" 4	3.0	
27	" 4	1.5	
28	" 6	3.0	
29	" 4	1.5	
30	" 4	1.5	
31	10 A.M. 3 P.M. 6 7	4.0	●—6 P.M.
1944 Jan. 1	A.M. 5	3.0	
2	" 4	1.5	
3	" 4	1.5	
4	" 5	1.5	
5	" 4	1.5	
6	" 5	1.5	
7	" 4	1.5	
8	" 8	3.0	Menstruation—(Jan. 8 to 11)
9	" 4	1.5	
10	" 4	1.5	
11	" 4	1.5	
12	" 4	1.5	
13	" 4	1.5	
14	" 4	1.5	●—6 P.M.
15	" 5	3.0	
16	" 4	1.5	●—2:30 P.M.
17	" 5	1.5	●—9 A.M. and 2 P.M.
18	" 4	1.5	
19	" 6	3.0	
20	" 6	3.0	
21	" 4	1.5	
22	" 4	1.5	
23	" 4	0.5*	●—4:30 A.M. *All day
24	" 4	1.5	
25	" 5	1.5	
26	" 4	1.5	
27	" 4	1.5	
28	4 P.M. 6 P.M. 4	3.0	
29	8 A.M. 4	1.5	
30	6 P.M. A.M. 8	4.0	●—6 P.M.
31	" 8		●—9 A.M.
Feb. 1	" 4	1.5	
2	" 6	3.0	

# PETIT MAL TYPES OF EPILEPSY—SPANGLER

TABLE I. URINARY pH AND RECORD OF SEIZURES (Continued)

November 20, 1943-March 13, 1944

Date 1944	1st A.M. or other hour specimen  Urinary pH	Total Amount Taken Daily in 3 Doses, after Meals.† Gms.	Record of Seizures and Comment
Feb. 3	" 4	2.0	
4	" 5	1.5	
5	" 4	1.5	●—6 P.M. Menstruation— (Feb. 5 to 9)
6	" 4	1.5	
7	" 6	3.0	
8	" 4	1.5	
9	" 6	3.0	
10	" 4	1.5	
11	" 4	1.5	●—9 A.M.
12	" 4	1.5	
13	" 6	3.0	From Feb. 14 the pH was taken both on arising and retiring
14	" 6	4.0	●—7 P.M.
	P.M. 4		
15	A.M. 6	4.0	
	P.M. 8		
16	A.M. 4	1.5	
17	" 4	5.0	
	P.M. 8		
18	A.M. 4	2.5	
	P.M. 8		●—1:30 P.M.
19	A.M. 4	2.5	
	P.M. 8		
20	A.M. 4	2.5	
	P.M. 6		
21	A.M. 6	4.0	
	7 P.M. 4		○—6:30 P.M.
22	11 P.M. 8		
23	A.M. 6	3.0	
	" 4	1.5	
24	" 8	4.0	
	P.M. 8*		*Soda bicarbonate for indigestion
25	A.M. 8	3.0	
26	" 8	1.5	
27	" 4	1.5	
28	A.M. 5	3.0	
29	" 6	2.5	
	P.M. 4		○—4:30 P.M.
Mar. 1	A.M. 4	3.0	
	P.M. 4		
2	A.M. 4	1.5	
	P.M. 4		●—6:30 P.M.
3	A.M. 4	1.5	
4	" 4	2.5	●—7 P.M. Menstruation—(Mar. 4 to 7)
	P.M. 4		
5	A.M. 4	2.5	●—7:30 A.M.
	P.M. 8		
6	A.M. 4	1.5	
7	" 4	1.5	
	P.M. 4		
8	A.M. 4	1.5	●—4 P.M.
9	" 4	2.5	
	P.M. 6		
10	A.M. 4	1.5	
11	" 4	2.5	
	P.M. 6		
12	P.M. 4	1.5	○—6 P.M.
13	A.M. 6	3.0	○—3 P.M.

†dl-Glutamic Acid  
Hcl. Caps. 0.5 Gm. each (Lederle).

Type of Seizures

●—Hazy Attack

○—Petit Mal

x—Grand Mal

*Summarized Deductions (Table I):* dl-Glutamic Acid Hydrochloride in capsules of 0.5 gm. each were given in three daily doses, totaling in amounts that ranged from 1.5 to 4.5 grammes per day from November 20, 1943, to March 13, 1944.

A urinary pH of 5 or above occurred on 55 days during this period of 114 days, 48% of the days.

Four menstrual periods occurred during these 114 days, and during the days of the four periods the pH of the urine was 5 or above twelve times, 10 per cent of the days during menstruation.

During these twelve times with a pH of 5 or above, six "hazy" manifestations occurred, two of them on the day menstruation began. There were no petit mal or convulsive seizures.



# PETIT MAL TYPES OF EPILEPSY—SPANGLER

TABLE II. URINARY pH AND RECORD OF SEIZURES  
March 14, 1944-April 24, 1944

Date 1944	1st A.M. or other hour specimen Urinary pH	Total Amount tak- en Daily in 3 doses, after meals.† Gms.	Record of Seizures and Comment
Mar. 14	A.M. 5	4.64	<i>Note change in type and dosage of Glutamic Acid (from dl-Glutamic Acid to d-Glutamic Acid).</i>  ●—6:30 P.M.  ●— 2 P.M. ●—10 A.M.
15	P.M. 8		
	A.M. 4	4.64	
	P.M. 4		
16	A.M. 4	4.64	
	P.M. 4		
17	A.M. 4	4.64	
	P.M. 8		
18	A.M. 4	4.64	
	P.M. 8		
19	A.M. 6	4.64	
20	A.M. 4	4.64	
	P.M. 4		
21	A.M. 4	6.96	
	P.M. 6		
22	A.M. 6	6.96	
	P.M. 6		
23	A.M. 4	6.96	
	P.M. 8		
24	A.M. 8	6.96	
	P.M. 6		
25	A.M. 6	6.96	
	P.M. 8		
26	A.M. 4	6.96	
	P.M. 6		
27	A.M. 6	6.96	
28	A.M. 4	11.6	
	P.M. 6		
29	A.M. 4	11.6	
	P.M. 4		
30	A.M. 4	11.6	
	P.M. 4		
31	A.M. 4	11.6	
	P.M. 4		
Apr. 1	A.M. 4	11.6	Menstruation—(Apr. 2 to 7)
	P.M. 4		
2	A.M. 4	11.6	
	P.M. 4		
3	A.M. 4	11.6	
	P.M. 4		
4	A.M. 4	11.6	
	P.M. 4		
5	A.M. 4	11.6	
	P.M. 4		
6	A.M. 4	11.6	
	P.M. 6		
7	A.M. 4		
	P.M. 4	11.6	
8	A.M. 4		
	P.M. 4	11.6	

uary, 1937, until September, 1940 (forty-four months), twenty-five grand mal and 181 petit mal seizures were recorded.

September, 1940, dilantin sodium was started in combination with phenobarbital. From this date until March 30, 1941 (six months), the attacks lessened and there were only three grand mal and nineteen petit mal seizures recorded.

March 31, 1941, when I first saw the patient, crotalin solution intramuscularly was begun for its nonspecific protein reaction (soil alteration).

Weichardt<sup>17</sup>, one of the fathers of immunology, explained the non-specific protein reaction as a cell-stimulating and plasma-activating effect, and, in a personal letter to me under date of November 13, 1925, in referring to an article of mine published September 16, 1925, states: "I see from your article on 'Nonspecific Therapy in Sensitization Diseases' in the

TABLE II. URINARY pH AND RECORD OF SEIZURES (Continued)  
March 14, 1944-April 24, 1944

Date 1944	1st A.M. or other hour specimen Urinary pH	Total Amount tak- en Daily in 3 doses, after meals.† Gms.	Record of Seizures and Comment
Apr. 9	A.M. 4	11.6	°—10:30 A.M.
	P.M. 4		
10	A.M. 4	11.6	
	P.M. 4		
11	A.M. 4	11.6	
	P.M. 4		
12	A.M. 4	11.6	●— 8 A.M.
	P.M. 6		
13	A.M. 4	11.6	●— 7:45 A.M.
	P.M. 5		●— 6 P.M.
14	A.M. 4	11.6	●—10 A.M.
	P.M. 6		
15	A.M. 4	11.6	
	P.M. 4		
16	A.M. 4	11.6	
	P.M. 4		
17	A.M. 4	11.6	
	P.M. 4		
18	A.M. 4	11.6	
	P.M. 4		●— 2 P.M.
19	A.M. 4	11.6	
	P.M. 4		
20	A.M. 4	11.6	
	P.M. 4		
21	A.M. 4	11.6	
	P.M. 4		
22	A.M. 4	11.6	
	P.M. 4		
23	A.M. 4	11.6	
	P.M. 4		°— 3 P.M.
24	A.M. 4	11.6	
	P.M. 4		

†*d*-Glutamic Acid  
Hcl. Caps. 0.58 Gm. each (Lederle)

*Summarized deduction* (Table II): *d*-Glutamic Acid Hydrochloride in capsules of 0.58 gm. each were given in three daily doses, totaling in amounts ranging from 4.6 to 11.6 grammes per day from March 14 to April 24, 1944.

A urinary pH of 5 or above occurred on twenty days during this period of forty-two days, 47.6 per cent of the days.

One menstrual period occurred during these forty-two days and the pH of the urine was above 4 only once, approximately 0.5 per cent of the days during menstruation. During this menstruation (April 2 to 7), two petit mal seizures occurred, both on the last day of the menstrual period.

No "hazy" attacks or convulsions occurred.

*New York Medical Journal and Record* that you have earlier turned in at the right path."

Starkenstein<sup>16</sup> had also shown in 1919 that alteration of the permeability of cell membranes was an important factor in the nonspecific protein reaction. Peterson<sup>9</sup>, quoting the findings of both of these investigators, refers to the alterative effect of nonspecific protein reactions on enzymes<sup>9</sup>, and Kolmer<sup>6</sup>, discussing one of my papers, pointed to the possible effect on colloidal modification of nonspecific protein reactions.

Essex and his associates<sup>4</sup>, in studying the physiological action of crotalin, conclude its effect is largely due to peripheral vascular dilatation. Recently, Seyle<sup>11</sup>, Code<sup>2</sup>, Dragstedt<sup>3</sup>, Landis<sup>7</sup>, and others all have stressed the alteration of cell permeability in anaphylactic shock and allergy.

# PETIT MAL TYPES OF EPILEPSY—SPANGLER

TABLE III. URINARY pH AND RECORD OF SEIZURES  
April 25, 1944-May 8, 1944

Date 1944	1st A.M. or other hour specimen.  Urinary pH	Total Amount Taken Daily in 5 Doses, After Meals.† Gms.	Record of Seizures and Comment
Apr. 25	A.M. 4	10.0	Note change to Natural Dextrorotatory Glutamic Ac.d Tablets (P.D. & Co.), for 14 days.
	P.M. 8		
26	A.M. 4	10.0	
	P.M. 8		
27	A.M. 6	10.0	
	P.M. 6		
28	A.M. 4	10.0	
	P.M. 6		
29	A.M. 6	10.0	
	P.M. 4		
30	A.M. 4	10.0	
	P.M. 8		
May 1	A.M. 8	10.0	
	P.M. 6		
2	A.M. 6	10.0	Menstruation— (May 1 to 5) °—5 P.M.
	P.M. 6		
3	A.M. 4	10.0	°—10 P.M.
	P.M. 4		
4	A.M. 4	10.0	
	P.M. 4		
5	A.M. 4	10.0	
	P.M. 4		
6	A.M. 4	10.0	
	P.M. 4		
7	A.M. 4	10.0	
	P.M. 4		
8	A.M. 4	10.0	●— 4 P.M. ●—6 P.M.
	P.M. 4		

†Natural Dextrorotatory Glutamic Acid Tablets, 0.5 Gm. each (P.D. & Co.)

*Summarized Deductions (Table III):* Natural Dextrorotatory Glutamic Acid tablets of 0.5 gm. each were started. (The tablets, instead of the larger 0.58 gm. capsules, seemed easier to take.) These were taken, 10 grammes per day in three divided doses from April 25 to May 8, 1944.

A urinary pH of 5 or above was present on eight of the fourteen days, 57 per cent of the days, when the tablets were being used.

A menstrual period occurred May 1 to 6, during which two petit mal attacks occurred, on May 1 and May 3, respectively. Two "hazy" attacks followed on May 8.

While the combined crotalin-dilantin-phenobarbital therapy controlled the major seizures in this patient, the petit mal type continued, even when lessened in frequency and, at times, in severity. From March 31, 1941, to December 1, 1944 (forty-four months), under anticonvulsant medication orally and crotalin intramuscularly, *no major seizures* occurred. The petit mal seizures were also lessened in frequency and many of them were described as a "haziness" without, as her family often thought, loss of consciousness. While from March 30, 1941, to November 20, 1943 (thirty-two months), prior to the start of glutamic acid medication, there were no convulsions, there occurred as recorded a total of eighty-six petit mal attacks and forty-eight "hazy" manifestations.

With the absence of major attacks for forty-four months but with the continuance of the petit mal type, even though lessened in number, this patient, through her intelligent co-operation, seemed an appropriate one in whom to use glutamic acid after the method suggested by Price, Waelsch and Putnam.<sup>10</sup> Accordingly, from November 20, 1943, to November 20, 1944, glutamic acid in one form or another of its two racemized forms, or dextrorotatory glutamic acid, was administered in various amounts in addition to dilantin sodium orally, 4½ grains daily, and crotalin solution intramuscularly, gr. 1/75, at bi-weekly intervals. A part of the time ½

grain of phenobarbital was also taken once a day. During this one-year period (November 20, 1943, to November 20, 1944) a total of thirty-one petit mal attacks and thirty-nine "hazy" manifestations occurred, which was about half the number recorded the previous year.

#### EFFECT OF GLUTAMIC ACID ON THE URINARY PH AND ON THE PETIT MAL TYPE OF SEIZURES

The patient made her own daily urinary pH determinations with "Alk-acid" test paper, matched with a colorimetric scale, both of which were supplied by the Fisher Scientific Company of Pittsburgh and St. Louis.

This method of recording the pH has been reported to be quite satisfactory and uniformly accurate as a universal indicator for hydrogen ion concentration. We have checked sixty-two of these colorimetric determinations against accurate electric potential determinations. This check has shown the relative degree of acidity to be approximately within a  $\frac{1}{2}$  pH unit, when compared with the electric potential determination.

For more detailed and accurate interpretation of the effect of glutamic acid on the urinary pH and petit mal seizures, a study and analysis of the daily records is submitted in the five accompanying tables.

#### SUMMARY OF FINDINGS RECORDED IN THE TABLES

Glutamic acid in four forms was administered, and the daily amount given recorded, to a female adult epileptic patient who had been rendered free from major (convulsive) seizures with anticonvulsant medication orally and crotalin intramuscularly for forty-four months, but in whom the petit mal attacks were only slightly affected and tended to recur, especially at or near the menstrual period. The pH of the urine was determined and recorded on arising each morning, and a part of the time also at night, for one year. The petit mal seizures and so-called "hazy" attacks are also noted in the five tables

TABLE I records the daily use of *dl*-glutamic acid hydrochloride, in capsule form, in varying amounts ranging from 1.5 gm. to 4.5 gm. daily. During this period of 114 days a 4 pH of the urine was present on fifty-nine days, or 52 per cent of the time. During these 114 days on *dl*-glutamic acid hydrochloride four petit mal attacks and twenty-one "hazy" manifestations occurred.

TABLE II and TABLE IV record the daily use of *d*-glutamic acid hydrochloride, in capsule form, in daily amounts ranging from 4.64 gm. to 11.6 gm. During these periods of 121 days a 4 pH of the urine was present on eighty-nine days, or 73 per cent of the time. In these 121 days, eleven petit mal seizures and eleven "hazy" manifestations occurred.

TABLE III records the daily use of natural dextrorotatory glutamic acid, in tablet form (Parke, Davis & Co.) in the amount of 10 gm. per day for fourteen days. During this two-week period, a 4 pH of the urine was present on six of the fourteen days, or 43 per cent of the time. Two petit mal attacks and two "hazy" manifestations occurred.

# PETIT MAL TYPES OF EPILEPSY—SPANGLER

TABLE IV. URINARY pH AND RECORDS OF SEIZURES  
May 9, 1944—July 28, 1944

Date 1944	1st A.M. or other hour specimen.  Urinary pH	Total Amount Taken Daily in 5 Doses, After Meals.† Gms.	Record of Seizures and Comment
May 9	A.M. 6	11.6	Note return to d-Glutamic Acid Hydrochloride capsules, and increased daily amount taken.
	P.M. 4		
10	A.M. 4	11.6	
	P.M. 4		
11	A.M. 4	11.6	
	P.M. 4		
12	A.M. 4	11.6	●—8:15 A.M.
	P.M. 4		
13	A.M. 4	11.6	
	P.M. 4		
14	A.M. 4	11.6	●—6 P.M. ●—9:15 A.M. ●—10:30 A.M.
	P.M. 4		
15	A.M. 4	11.6	
	P.M. 4		
16	A.M. 4	11.6	
	P.M. 4		
17	A.M. 4	11.6	
	P.M. 4		
18	A.M. 4	8.7	
	P.M. 4		
19	A.M. 4	8.7	
	P.M. 4		
20	A.M. 4	8.7	
	P.M. 4		
21	A.M. 4	8.7	
	P.M. 4		
22	A.M. 4	8.7	
	P.M. 4		
23	A.M. 4	8.7	
	P.M. 4		
24	A.M. 4	8.7	
	P.M. 4		
25	A.M. 4	8.7	
	P.M. 4		
26	A.M. 4	8.7	
	P.M. 4		
27	A.M. 4	8.7	Menstruation— (May 27 to 31)
	P.M. 4		
28	A.M. 4	8.7	
	P.M. 4		
29	A.M. 4	8.7	
	P.M. 4		
30	A.M. 4	8.7	
	P.M. 4		
31	A.M. 4	8.7	
	P.M. 4		
June 1	A.M. 4	8.7	
	P.M. 4		
2	A.M. 4	8.7	
	P.M. 4		
3	A.M. 4	8.7	
	P.M. 4		
4	A.M. 4	8.7	
	P.M. 4		
5	A.M. 5	5.22	
	P.M. 5		
6	A.M. 4	5.22	
	P.M. 4		
7	A.M. 4	5.22	
	P.M. 4		
8	A.M. 4	5.22	
	P.M. 4		
9	A.M. 4	5.22	
	P.M. 4		
10	A.M. 4	8.7	°—9 A.M. °—6 P.M.
	P.M. 4		
11	A.M. 4	5.8	°—2 P.M.
	P.M. 4		
12	A.M. 4	5.8	
	P.M. 4		
13	A.M. 4	5.8	
	P.M. 4		
14	A.M. 4	5.8	
	P.M. 4		
15	A.M. 4	5.8	°—10 A.M.
	P.M. 4		
16	A.M. 4	5.8	°—10 A.M. °—2 P.M.
	P.M. 4		
17	A.M. 4	5.8	
	P.M. 4		
18	A.M. 4	5.8	
	P.M. 4		

# PETIT MAL TYPES OF EPILEPSY—SPANGLER

TABLE IV. URINARY pH AND RECORD OF SEIZURES (Continued)

May 9, 1944-July 28, 1944

Date 1944	1st A.M. or other hour specimen  Urinary pH	Total Amount Taken Daily in 3 Doses, after Meals.† Gms.	Record of Seizures and Comment
June 19	A.M. 4	5.8	Menstruation— (June 23 to 27)  °— 7:30 A.M.
	P.M. 4		
20	A.M. 4	5.8	
	P.M. 4		
21	A.M. 5	5.8	
	P.M. 4		
22	A.M. 4	5.8	
	P.M. 4		
23	A.M. 4	5.8	
	P.M. 4		
24	A.M. 4	5.8	
	P.M. 4		
25	A.M. 4	5.8	
	P.M. 4		
26	A.M. 4	5.8	
	P.M. 4		
27	A.M. 4	5.8	
	P.M. 4		
28	A.M. 4	5.8	
	P.M. 4		
29	A.M. 4	5.8	
	P.M. 4		
30	A.M. 4	5.8	
	P.M. 4		
July 1	A.M. 4	5.8	
	P.M. 4		
2	A.M. 4	5.8	
	P.M. 4		
3	A.M. 6	5.8	
	P.M. 4		
4	A.M. 4	5.8	
	P.M. 4		
5	A.M. 4	5.8	
	P.M. 4		
6	A.M. 4	5.8	
	P.M. 4		
7	A.M. 4	5.8	
	P.M. 4		
8	A.M. 4	5.8	
	P.M. 4		
9	A.M. 4	5.8	
	P.M. 4		
10	A.M. 4	5.8	
	P.M. 4		
11	A.M. 4	5.8	
	P.M. 4		
12	A.M. 4	5.8	
	P.M. 4		
13	A.M. 6	5.8	
	P.M. 4		
14	A.M. 4	5.8	
	P.M. 4		
15	A.M. 4	5.8	
	P.M. 4		
16	A.M. 6	5.8	
	P.M. 4		
17	A.M. 4	5.8	
	P.M. 4		
18	A.M. 4	5.8	
	P.M. 4		
19	A.M. 4	5.8	
	P.M. 4		
20	A.M. 5	5.8	
	P.M. 4		
21	A.M. 4	5.8	Menstruation— (July 22 to 26)
	P.M. 4		
22	A.M. 4	8.12	
	P.M. 8		
23	A.M. 6	5.8	
	P.M. 4		
24	A.M. 4	5.8	
	P.M. 4		
25	A.M. 4	5.8	
	P.M. 4		
26	A.M. 4	5.8	
	P.M. 6		
27	A.M. 6	5.8	
	P.M. 6		
28	A.M. 4	None	
	P.M. 6		

*Summarized Déductions (Table IV):* *d*-Glutamic Acid in Hydrochloride in capsule form, 0.58 gm. each, were resumed, as the tablets in this racemized form were not being manufactured. The *d*-Glutamic Acid Hydrochloride was then continued for eighty days (May 9 to July 28, 1944), in doses of 5.22 gm., 5.8 gm. 8.7 gm. and 11.6 gm. daily in three equally divided doses of each. The varied amount taken daily was due to an effort to determine the smallest daily dose in order to maintain a urinary pH of 4, and to lessen the large number of capsules, for which the patient began to have a dislike.

During the eighty days, when the daily dosage was varied and reduced, the urinary pH was above 4 on twelve days out of the eighty, or 14.7 per cent of the days. Three menstrual periods occurred, during which time the urinary pH rose to 5 or above on two days only.

During these three menstrual periods while the *d*-Glutamic Acid Hydrochloride form was being used, over the eighty-day period there was only one petit mal attack which occurred during a menstrual period, and there were no "hazy" manifestations or convulsive seizures. (During the entire time when *d*-Glutamic Acid Hydrochloride was taken daily, 121 days, the pH of the urine was 5 or above on thirty-two days, 26 per cent of the days. (Tables II and IV together.)

There were no seizures in any form from May 14 to June 10, 1944. On June 10, 11, 15 and 16 petit mal attacks occurred which were independent of any menstrual influence. However, five days previous to the petit mal attack on June 10, *d*-Glutamic Acid Hydrochloride had been reduced in dosage from 8.7 to 5.22 grammes per day. The urinary pH remained at 4 for fifty-three days (June 5 to July 28) with exception of thirteen days, 24.5 per cent of the days. A daily amount of 5.8 gm. (15 capsules of 0.58 gm. each), were continued until July 28, when the patient ran out of the *d*-Glutamic form for twenty-four hours.

TABLE V records the daily use of "Glutan H-C-L"-Lederle (glutamic acid hydrochloride in capsule form), in amounts ranging from 3.888 gm. to 7.5 gm. per day. During 102 days of this time a 4 pH of the urine was present on forty-eight days, or 47 per cent of the time. Nine petit mal and ten "hazy" manifestations occurred. The patient then ran out of capsules from August 27 to September 8, 1944 (twelve days), and during the last five of these twelve days without any Glutan H-C-L 4 petit mal, no "hazy," attacks occurred and the pH of the urine rose to eight on one day, six on five days, five on one day and a pH of 4 was present only on four of the twelve days.

#### CLINICAL RESULTS

The administration of glutamic acid or one of its modifications or racemizations, used daily over a period of one year, in conjunction with crotalin intramuscularly and dilantin orally, was beneficial in lessening the frequency of petit mal type of seizures, and appreciably modifying their severity. The amount of acid administered was guided by a daily recording of the urinary pH in an effort to keep the hydrogen ion concentration (pH) below 5.

The petit mal type of seizure was little modified by the combined alterative and anticonvulsant action of crotalin and dilantin, although the convulsive seizures were absent for forty-four months. During the year (November 20, 1943, to November 20, 1944) when glutamic acid was added to the medication, petit mal seizures occurred twenty-seven times and there were so-called "hazy" symptoms recorded on forty-five days. It is of especial interest to note in Table V that with no glutamic acid

taken for twelve days the hydrogen ion concentration of the urine rose, after the third day, rather consistently each day to a 6 pH. Also, that during the last five days without acid, five petit mal seizures occurred. This increase of seizures with no glutamic acid followed a ten-week interval of entire freedom from any type of seizure. The previous year both types of petit mal seizures had occurred thirty-nine and fifty-one times, respectively.

During or near the time of a menstrual period throughout the year, minor forms of attacks were absent only three times. At these three periods a urinary pH of 5 or 4 was present. At each of the other nine periods of the year, petit mal or "hazy" manifestations appeared, and a urinary pH of 6, 7 or above was present.

Throughout the year (November 20, 1943, to November 20, 1944) while taking one or another form and amount of glutamic acid daily there occurred twenty-seven petit mal seizures (two at time of periods) and forty-five "hazy" manifestations (thirty-one of which occurred at time of periods), thus only fourteen "hazy" attacks occurred during the year while glutamic acid was being used and when the influence of the menstruation was not a factor.

#### COMMENT

It has been a general experience that anticonvulsants (bromide, phenobarbital, dilantin sodium) are of much value in modifying, to a greater or less extent, recurrent convulsive seizures (grand mal type of epilepsy).

The minor form, or petit mal type of seizure, has, however, rather uniformly been persistently resistant in many patients, to all forms of anticonvulsant medication.

The case report herewith submitted illustrates the usefulness of altering metabolism in an epileptic patient by biological intramuscular therapy which, in my experience, frequently has been a decided adjuvant to anticonvulsive treatment.

As is shown in the detailed data in this case report, and in the experience of Price and Waelsch<sup>10</sup>, anticonvulsants have but a limited beneficial effect on petit mal type of seizures. The effect of crotalin solution intramuscularly in altering metabolism I have found for many years beneficial, at times alone, or combined with anticonvulsant therapy. However, even with the biological alterative effect of crotalin, the petit mal seizures are less influenced than the grand mal type of attack.

Naturally, a question arises: Do both forms of these clinical manifestations arise from a common cause—is there a trigger mechanism of common origin? In my clinical experience patients with predominantly minor manifestations of momentary lapses are the ones having a greater percentage of allergic backgrounds. The symptom complex of disturbed metabolism in allergic patients and in epileptics have much in common—including low gastric acidity with gastrointestinal disturbances (hypersensitivity) and, at times, an eosinophilia; frequently an alkaline urine.



# PETIT MAL TYPES OF EPILEPSY—SPANGLER

TABLE V. URINARY pH AND RECORD OF SEIZURES

July 29, 1944–November 20, 1944

Date 1944	1st A.M. or other hour specimen.  Urinary pH	Total Amount Taken Daily in 3 Doses, after meals.† Gms.	Record of Seizures and Comment
July 29	A.M. 4	3.888	Note change to stocked form of capsules, "Glutan" H-C-L.
	P.M. 4		
30	A.M. 4	5.832	
	P.M. 4		
31	A.M. 4	5.832	
	P.M. 4		
Aug. 1	A.M. 6	5.832	
	P.M. 4		
2	A.M. 4	5.832	
	P.M. 4		
3	A.M. 4	5.832	
	P.M. 4		
4	A.M. 4	5.832	
	P.M. 4		
5	A.M. 4	5.832	
	P.M. 4		
6	A.M. 4	5.832	
	P.M. 4		
7	A.M. 4	5.832	
	P.M. 4		
8	A.M. 4	5.832	
	P.M. 4		
9	A.M. 4	5.832	
	P.M. 4		
10	A.M. 4	5.832	
	P.M. 4		
11	A.M. 4	5.832	
	P.M. 4		
12	A.M. 4	5.832	
	P.M. 4		
13	A.M. 4	5.832	
	P.M. 4		
14	A.M. 4	5.832	
	P.M. 4		
15	A.M. 4	5.832	
	P.M. 4		
16	A.M. 4	5.832	
	P.M. 4		
17	A.M. 4	5.832	Menstruation— (Aug. 17 to 21) *Soda bicarbonate for in- digestion
	P.M. 8		
18	A.M. 8*	5.832	
	P.M. 4		
19	A.M. 4	5.184	
	P.M. 4		
20	A.M. 4	5.184	
	P.M. 4		
21	A.M. 4	3.888	
	P.M. 4		
22	A.M. 5	3.888	
	P.M. 4		
23	A.M. 4	3.888	
	P.M. 5		
24	A.M. 4	3.888	
	P.M. 5		
25	A.M. 5	2.916	
	P.M. 4		
26	A.M. 5	2.916	
	P.M. 6		
27	A.M. 6	None	No Glutamic capsules from Aug. 27 to Sept. 8
	P.M. 8		
28	A.M. 4	"	
	P.M. 4		
29	A.M. 4	"	
	P.M. 4		
30	A.M. 4	"	
	P.M. 4		
31	A.M. 6	"	
	P.M. 6		
Sept. 1	A.M. 6	"	
	P.M. 6		
2	A.M. 6	"	
	P.M. 6		
3	A.M. 4	"	°—11 A.M.
	P.M. 6		
4	A.M. 4	"	°— 9:30 A.M. °— 7 P.M.
	P.M. 4		
5	A.M. 6	"	°—1:30 P.M.
	P.M. 4		

# PETIT MAL TYPES OF EPILEPSY—SPANGLER

## TABLE V. URINARY pH AND RECORD OF SEIZURES (Continued)

July 29, 1944–November 20, 1944

Date 1943	1st A.M. or other hour specimen.  Urinary pH	Total Amount Taken Daily in 3 Doses, after Meals.† Gms.	Record of Seizures and Comment
Sept. 6	A.M. 5	"	
	P.M. 5		°— 2 P.M.
7	A.M. 4	"	
	P.M. 4		
8	A.M. 4	3.888	
	P.M. 4		●— 8 P.M.
9	A.M. 4	5.832	
	P.M. 4		
10	A.M. 4	5.832	●—11 A.M.
	P.M. 4		
11	A.M. 4	3.888	
	P.M. 4		
12	A.M. 4	5.832	
	P.M. 8*		*Ate tomatoes
13	A.M. 4	5.832	
	P.M. 5		
14	A.M. 4	5.832	
	P.M. 4		
15	A.M. 4	5.832	Menstruation—
	P.M. 4		Sept. 15 to 19
16	A.M. 4	5.832	
	P.M. 6		
17	A.M. 6	5.832	●—11:30 A.M.
	P.M. 6		
18	A.M. 4	3.888	
	P.M. 4		
19	A.M. 4	5.832	
	P.M. 4		
20	A.M. 4	5.832	
	P.M. 4		
21	A.M. 4	5.832	
	P.M. 4		
22	A.M. 4	5.832	
	P.M. 4		
23	A.M. 4	5.832	●— 2:30 P.M.
	P.M. 4		
24	A.M. 4	5.832	
	P.M. 4		●— 2 P.M.
25	A.M. 4	5.832	
	P.M. 4		
26	A.M. 4	5.832	
	P.M. 4		
27	A.M. 4	5.832	
	P.M. 6		
28	A.M. 4	5.832	
	P.M. 8		
29	A.M. 4	5.832	
	P.M. 4		
30	A.M. 4	5.832	
	P.M. 4		
<p>Note: There had been no seizures from June 25, a petit mal while in Maine on vacation, until Sept. 3 (72 days), at home after 17-hour auto trip (2 A.M. to 7 P.M.), and no Glutamic Acid Capsules from Aug. 27 to Sept. 8, 1944!</p>			
Oct. 1	A.M. 4	5.832	
	P.M. 4		
2	A.M. 4	5.832	
	P.M. 4		
3	A.M. 4	5.832	
	P.M. 8		°— 6:30 P.M.
4	A.M. 4	5.832	
	P.M. 4		
5	A.M. 4	5.832	
	P.M. 6		●— 6 P.M.
6	A.M. 5	5.832	
	P.M. 4		
7	A.M. 4	3.888	
	P.M. 8		●— 2:30 P.M.
8	A.M. 4	2.592	
	P.M. 4		
9	A.M. 6	2.592	
	P.M. 4		°— 7 P.M.
10	A.M. 4	2.592	
	P.M. 6		
11	A.M. 6	1.296	
	P.M. 5		
12	A.M. 4	None	Menstruation—
	P.M. 8		(Oct. 12 to 16)

# PETIT MAL TYPES OF EPILEPSY—SPANGLER

TABLE V. URINARY pH AND RECORD OF SEIZURES (Continued)

July 29, 1944-November 20, 1944

Date 1944	1st A.M. or other hour specimen.  Urinary pH	Total Amount Taken Daily in 3 Doses, after Meals.† Gms.	Record of Seizures and Comment
Oct. 13	A.M. 8 P.M. 8	"	
		"Glutan" caps. in- creased to 0.5 Gm. each	
14	A.M. 4 P.M. 4	6.0	
15	A.M. 4 P.M. 4	6.0	
16	A.M. 4 P.M. 4	6.0	
17	A.M. 4 P.M. 4	6.0	
18	A.M. 4 P.M. 4	6.0	°— 1:30 P.M.
19	A.M. 4 P.M. 4	6.0	
20	A.M. 4 P.M. 4	6.0	
21	A.M. 4 P.M. 6	6.0	
22	A.M. 5 P.M. 4	6.0	
23	A.M. 4 P.M. 5	6.0	
24	A.M. 4 P.M. 6	6.0	
25	A.M. 5 P.M. 6	6.0	°— 7 P.M.
26	A.M. 4 P.M. 4	6.0	°—11 P.M.
27	A.M. 4 P.M. 4	6.0	
28	A.M. 4 P.M. 4	6.0	
29	A.M. 4 P.M. 4	6.0	●— 1 P.M.
30	A.M. 4 P.M. 6	7.0	
31	A.M. 4 P.M. 4	7.5	
Nov. 1	A.M. 4 P.M. 4	7.5	
2	A.M. 4 P.M. 4	7.5	
3	A.M. 4 P.M. 4	6.0	
4	A.M. 4 P.M. 4	7.5	
5	A.M. 4 P.M. 4	7.5	
6	A.M. 4 P.M. 4	7.5	
7	A.M. 4 P.M. 4	7.5	
8	A.M. 4 P.M. 4	7.5	
9	A.M. 4 P.M. 4	6.0	
10	A.M. 4 P.M. 4	6.0	
11	A.M. 4 P.M. 4	6.0	
12	A.M. 4 P.M. 4	7.5	
13	A.M. 4 P.M. 4	7.5	
14	A.M. 4 P.M. 4	7.5	
15	A.M. 4 P.M. 4	7.5	°— 6 P.M.
16	A.M. 4 P.M. 4	6.0	
17	A.M. 4 P.M. 4	6.0	
18	A.M. 4 P.M. 4	4.0	
19	A.M. 4 P.M. 4	6.0	●— 8 P.M.
20	A.M. 4 P.M. 4	7.5	

†Glutamic Acid Hcl, Caps. 0.324 Gm. each. (Lederle)

*Summarized Deductions* (Table V): July 29, 1944, "Glutan" (Lederle), i.e., Glutamic Acid Hydrochloride capsules of 0.324 mgm. each were started. This form of Glutamic Acid Hydrochloride is regularly stocked and marketed for use in hydrochloric acid deficiency. I was interested to compare it with the *dl*-Glutamic and *d*-Glutamic Acid, and with the natural dextrorotatory form of glutamic acid, since they are less expensive than the racemized forms of glutamic acid.

"Glutan" capsules in daily amounts ranging from 3.888 gms. to 7.5 gms. were given for 102 days. A urinary pH of 5 or above, during this time, was present on fifty-four days, or 53 per cent of the time.

Three menstrual periods occurred during the 102 days "Glutan" capsules were being taken, no period having occurred during the twelve days the patient was without medication. During these three menstrual periods, the urinary pH was 5 or above one day during each period, and only one "hazy" manifestation occurred. However, after seven days without any glutamic medication, four petit mal seizures occurred on four successive days.

It is of special note that while the patient was vacationing in Maine, from June 7 to September 1, no seizures occurred except one petit mal type of attack June 25, during a menstrual period when the *d*-Glutamic acid hydrochloride capsules were still being used. She passed through the menstrual periods of July and August with no attacks, during which time she took *d*-Glutamic acid by hydrochloride capsules for eighty days and then began the "Glutan" capsules, (Tables IV & V), for 114 days, which completes the record for one year.

The tendency for petit mal symptoms to appear or be more aggravated at menstrual periods in the female, and at full moon in males (lunar month) is a common observation in various forms of allergy as well as in patients with petit mal types of epilepsy.

The beneficial effect of glutamic acid in lowering the pH of the urine in epilepsy as illustrated in this detailed case report, and the fact that menstruation, even when the patient is taking glutamic acid, often causes an increase in petit mal seizures, raises the question as to whether endocrine dysfunction may be less of a factor in the etiology of petit mal, than the increase of the hydrogen ion concentration (pH) of the urine during menstruation.

Finally, grand mal may result from a vascular sensitivity as suggested by various investigators, through an increased vascular permeability with an edema of the cerebral cortex and surrounding tissues, which may be a possible seat of the so-called "shock organ," while petit mal may result more from an altered immunologic (allergic) response as shown by a decreased hydrogen ion concentration of the urine.

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(References continued on Page 282)

# THE STUDY OF BRONCHIAL ASTHMA IN A GENERAL HOSPITAL

## With a Statistical Report of 200 Cases

MAJOR JACK A. RUDOLPH, MC, AUS

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BRONCHIAL asthma, its related conditions and complications, is responsible for an enormous morbidity in the Army. A survey of the recent literature on the subject reveals nothing new or startling. The most important of the newer writings, however, deal with the military aspects of bronchial asthma. In a survey of Allergy by French and Halpin<sup>6</sup> of the Fourth Service Command, covering a period from 1 November 1942 to 1 November 1943, it is disclosed that 8,139 allergic patients who were admitted to the hospital wards spent a total of 172,455 hospital days. This figure was approximately 10 per cent of the total hospital admissions in the Command for this period. Bronchial asthma was responsible for the greatest number of these admissions, as 5,447 patients, or 66.6 per cent, had this diagnosis. The scope and importance of allergy in the Army is further emphasized in papers by Crandall<sup>5</sup>, Lieder<sup>10</sup>, Hampton and Rand.<sup>7</sup>

The concept of allergy has increased our understanding and appreciation of the different agents which cause asthma. It has played an important role in the medical diagnosis of asthma and in the clinical differentiation of all who wheeze. As a result, the wheezing dyspnea of asthma may be more easily separated from many intrathoracic medical conditions. This includes such conditions as cardiac decompensation (cardiac asthma), fibroid tuberculosis, chronic bronchitis, aspirated foreign bodies, inflammations within the bronchi, Loeffler's syndrome, bronchial stenosis due to tumors, mediastinal tumors including neoplasms, substernal thyroid, persistent thymus, tuberculosis, aneurysms, trachio-bronchial glands, and Hodgkin's disease. On the basis of clinical history and physical examination, and complemented by laboratory studies and x-rays, little room for doubt is left as to the diagnosis of the type of wheezing being studied in the patient.

The disease, though chronic and rarely fatal in itself, is followed by pulmonary changes which ultimately incapacitate the soldier. These complications and sequelae can be prevented and symptomatic cure obtained if the medical officer is thoroughly aware of the facts and is so situated as to carry out the necessary studies and treatment with the view to the proper disposition of the asthmatic soldier.

For the purpose of clarity, the statistics in this report on the study of asthma in this general hospital, were governed largely by the allergic concept, and each case was evaluated on the basis of the following criteria:

(1) definition of asthma; (2) classification; and (3) specific criteria for the diagnosis of allergic asthma.

Presented before the Oliver Chapter of The Association of Military Surgeons, 23 March 1945.

# BRONCHIAL ASTHMA—RUDOLPH

TABLE I. CLASSIFICATION OF BRONCHIAL ASTHMA<sup>3</sup>

Allergen Antibody Stimulus		Allergen Demonstrable	Begins early in life. Family history positive. Other allergic manifestations common. Skin tests positive or allergen demonstrable by environmental control. Complete remission between attacks. No organic changes. Prognosis for relief and prevention of future attacks good. Seldom die of asthma. No effect on longevity.	
.....		EXTRINSIC		
Cholinergic Stimulus	H Substance Reaction in Bronchial Asthma	Allergen not Demonstrable	Begins around forty years of age. Family history usually negative. Other allergic manifestations uncommon. Skin tests negative. Allergen not demonstrable by environmental control. No complete remissions. Organic changes common. Prognosis for relief and prevention of future attacks—poor. Prognosis as to life—grave. Many die of asthma. Profound effect on longevity.	
.....		INTRINSIC		
Unknown Stimulus			Primary extrinsic with intrinsic complications	Organic Functional
		COMBINED EXTRINSIC and INTRINSIC	Primary intrinsic with extrinsic complications	Organic Functional

## DEFINITION

We define bronchial asthma as an affliction of the lower respiratory tract, characterized by recurring paroxysms of wheezing and dyspnea more pronounced in the expiratory phase, frequently associated with coughing and a sense of constriction in the chest, due to pathological and physiological changes of the bronchioles.

Asthma today is regarded by many as a manifestation of hypersensitivity of the bronchial tree. The cells of the bronchial mucous membrane have been conditioned to react in an abnormal manner when brought into contact with substances which are ordinarily harmless. The reaction and symptoms are the result of edema of the bronchial mucous membrane and the outpouring of secretion and its associated bronchospasm. It is possible that the edema occurs in an attempt to dilute the toxic material and prevent its formation on the surface or within the cell substance, and that the secretion is poured out to wash the irritant away. The mechanism of the bronchospasm is probably similar to spasm in any hollow viscus, and in asthma results in an attempt to dislodge the mucus plugs in the bronchioles which have been formed by the secretion and cellular debris.

## CLASSIFICATION

Many classifications of bronchial asthma may be found in the literature. The one used at this hospital has been based on the knowledge of the pathology of asthma, the mechanism involved in the pathology, and finally the symptoms produced as a result of these pathologic changes. My own experiences and studies during the past fifteen years have convinced me that bronchial asthma has a definite pathology regardless of the etiologic classification. This opinion is based in a great measure on the observations of

the histology of experimentally induced hypersensitive reactions in man, which was reported in 1932 by Kline, Cohen and Rudolph.<sup>8</sup> Recently Cohen<sup>3</sup> classified bronchial asthma, and since it covers essentially the same points used in our classification, it is shown herewith in Table I.

SPECIFIC CRITERIA<sup>2</sup>

In making the diagnosis of allergic from nonallergic asthmatic patients, the following points were considered:

1. In over half of the soldiers who have asthma there are allergic manifestations in collaterals or antecedents. However, specific hypersensitivity may not be transmitted and the asthmatic patient may have antecedents with eczema, with migraine, with vasomotor rhinitis as well as with bronchial asthma.

2. As a rule, the allergic soldier has more than one allergic manifestation. There may be combinations of asthma and hay fever, asthma and eczema, asthma and nonseasonal vasomotor rhinitis, occurring more often sequentially, but occasionally concurrently.

3. Symptoms usually start early in life, the onset past the age of fifty being relatively infrequent.

4. At the outset asthma is chiefly paroxysmal in character. Between attacks, for indefinite periods, the patient may be practically normal, presenting neither subjective nor objective symptoms. As the condition progresses, attacks follow more rapidly, and complications such as bronchitis or emphysema may eliminate all free intervals.

5. Acute asthmatic attacks are often preceded by allergic symptoms involving other systems or organs, by hay fever, vasomotor rhinitis, gastrointestinal disturbances or angioneurotic edema.

6. The most severe attacks usually occur at night while trying to sleep.

7. There is a tendency to periodicity in relation to the hour of the day or night, day of week or season of the year.

8. Orthopnea is frequently a prominent feature, even between paroxysms.

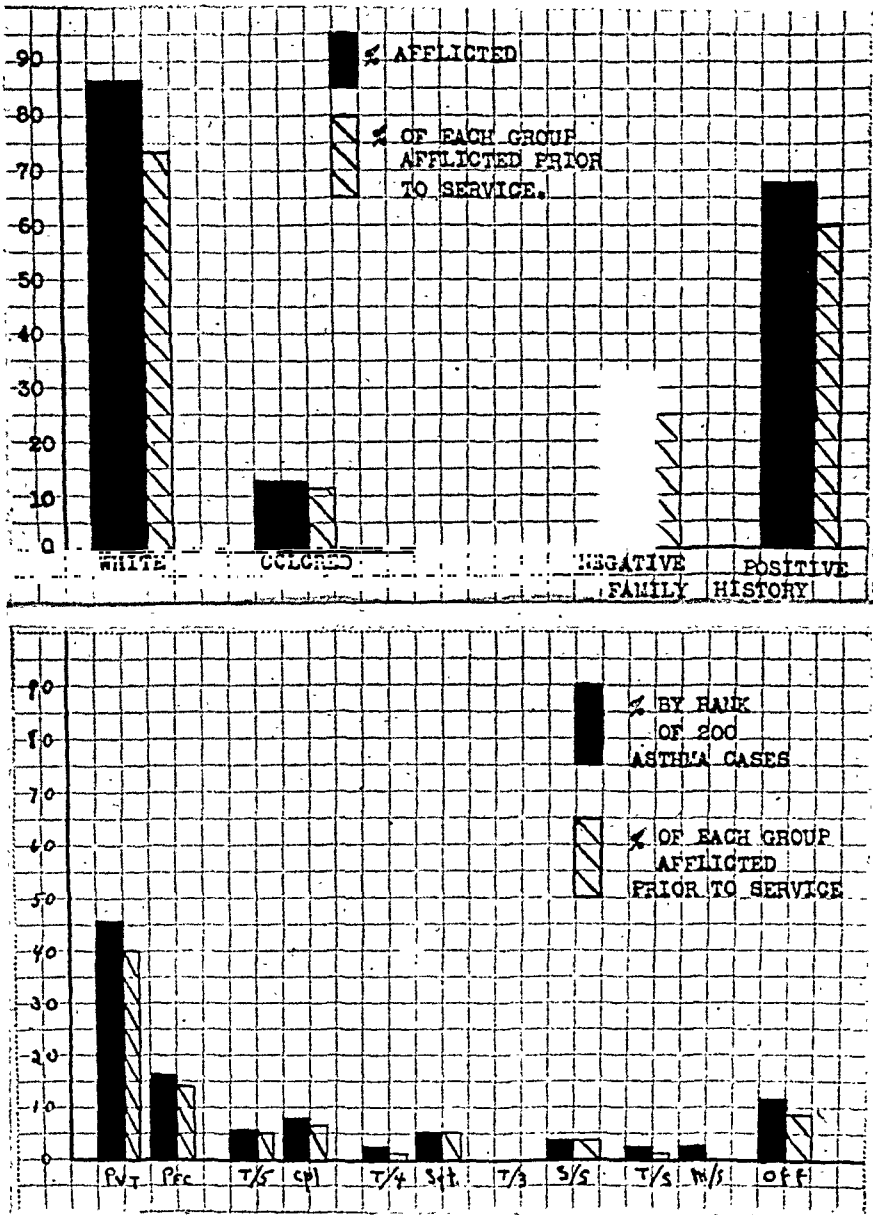
9. At first, emphysema is present only during the acute episodes; later it becomes a permanent feature in the physical findings.

10. Epinephrine in small doses will control the wheezing dyspnea in all cases except the most unusual ones.

11. If sputum is collected during or after an attack it may show Curschmann's spirals, Charcot-Leyden crystals, and frequently a high percentage of eosinophiles. A coincident blood and sputum eosinophilia is almost always a definite indication that allergy is the cause of the wheezing.

12. Positive skin tests help to identify the allergic soldier, but they do not necessarily make the etiologic diagnosis in all instances. Skin tests may err in two directions—frequently they are positive to allergens impossible to correlate with the clinical picture, and at times there are no skin reactions when the patient has symptoms from a particular

# BRONCHIAL ASTHMA—RUDOLPH



CHARTS 1 AND 2.

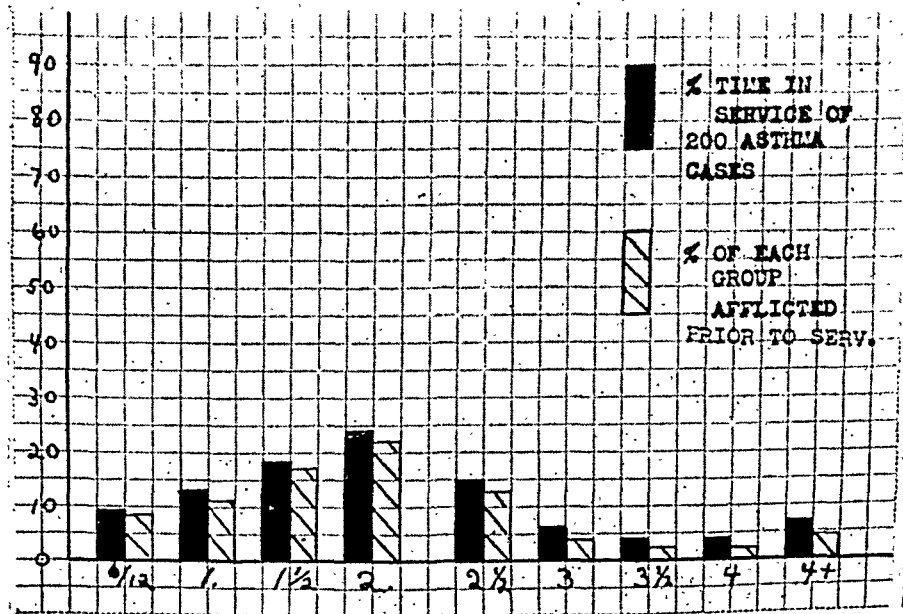
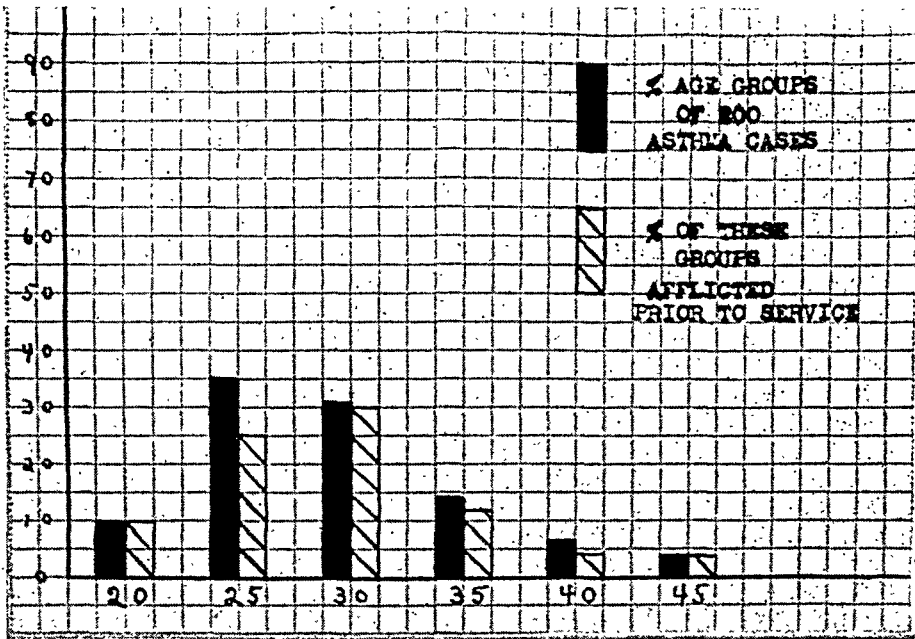
allergen. Positive skin tests to inhalants as a rule are clinically significant.

13. Finally, the patient with allergic asthma is chronically ill. One seldom dies from asthma, but there is an unusually high morbidity. If death does occur in the allergic group it is more often accidental, while the non-allergic, or intrinsic, asthmatics appear to have a definitely greater mortality.

## STATISTICAL SURVEY OF 200 CASES

This report, from the Allergy Section at Oliver General Hospital, is a review of 200 consecutively hospitalized asthmatic patients. It reveals that



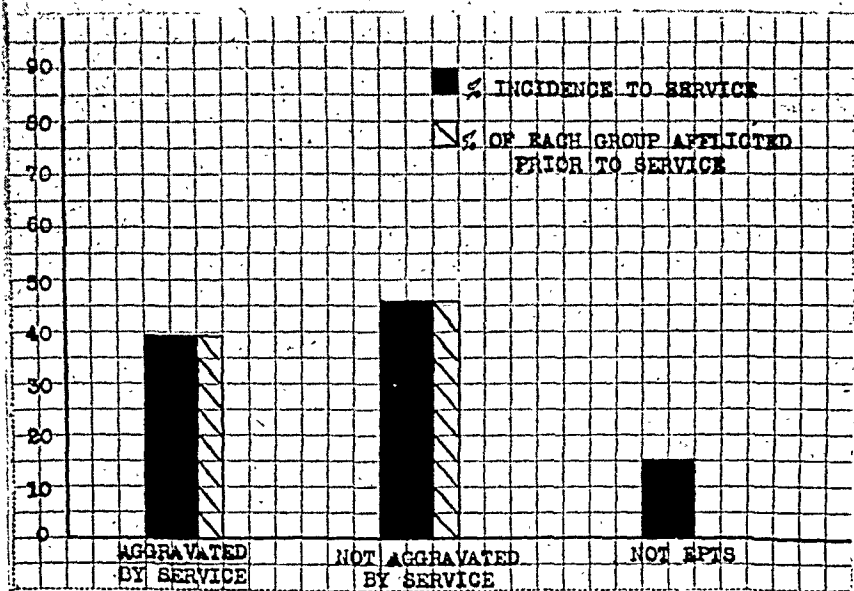
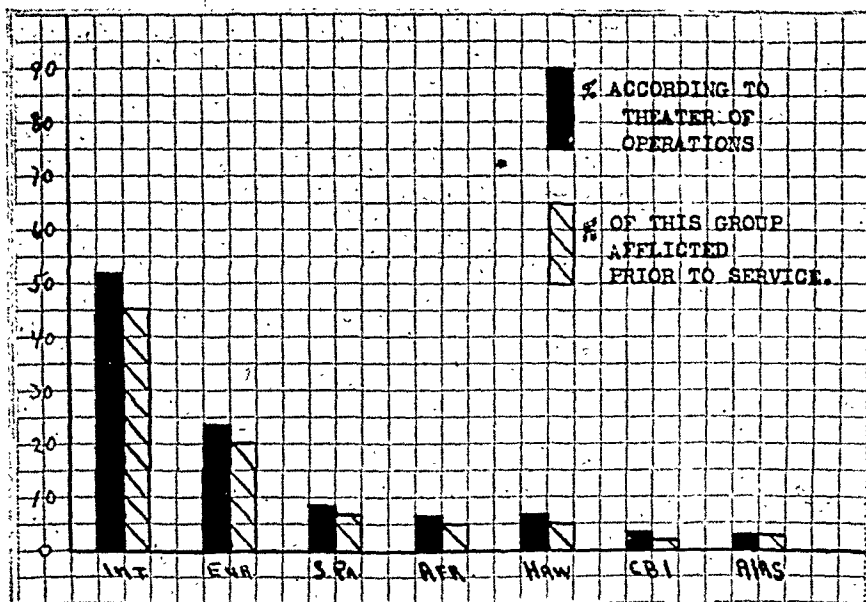


CHARTS 3 AND 4.

exacerbations, invalidizations and hospitalizations in overseas theatres are common, and that patients are frequently returned to the Zone of Interior. Often patients who had mild or infrequent attacks of asthma in the States developed attacks of asthma almost immediately upon arriving in foreign theatres of war and were unable to carry on with any type of duty. The importance of understanding this situation and knowing the vagaries of asthma will help one to properly classify and avoid sending many soldiers overseas who may break down and have severe asthmatic attacks. In this report the following information was obtained:

*Chart 1.*—This chart reveals that 174 patients, or 87 per cent of the

# BRONCHIAL ASTHMA—RUDOLPH

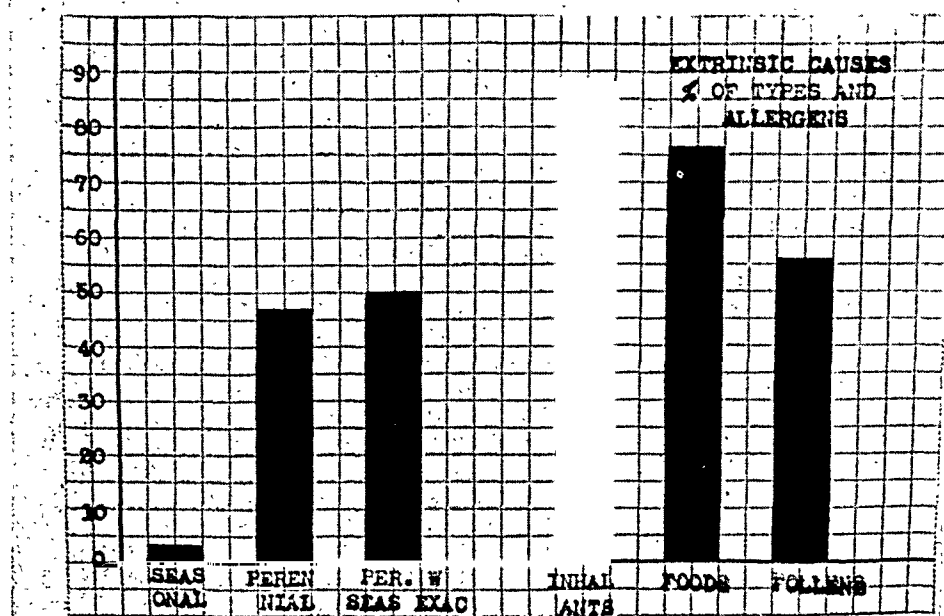
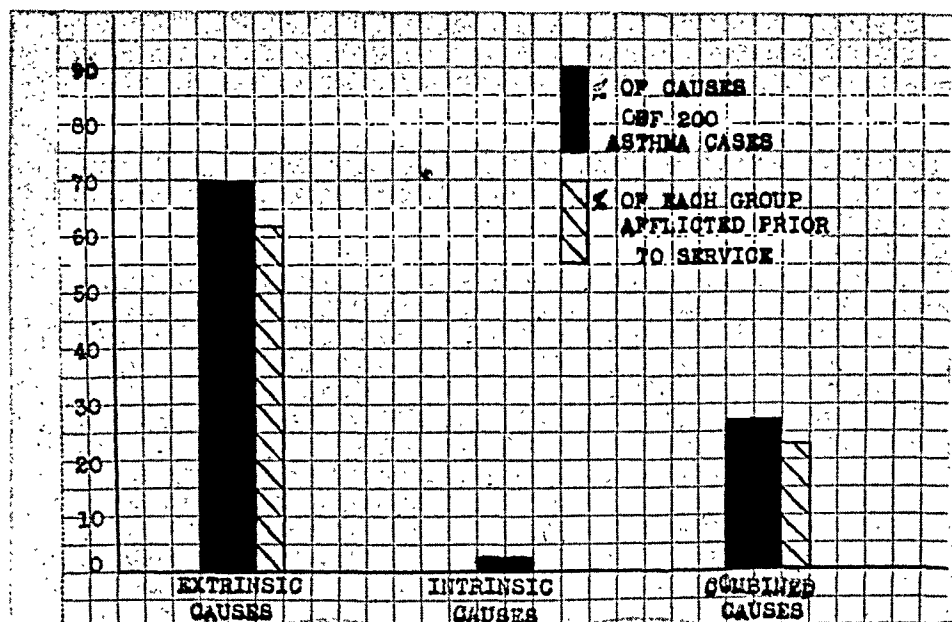


CHARTS 5 AND 6.

total, were white soldiers, and twenty-six patients, or 13 per cent, were negro soldiers. The family history was positive in 135 cases, or 67.5 per cent, and negative in sixty-five cases, or 32.5 per cent. There were no apparent differences in the onset or severity of the symptoms in either of these groups.

*Chart 2.* This chart reveals the distribution of asthma in the various grades in this series of 200 patients.

*Chart 3.* This chart points out the age range in soldiers with asthma. Twenty cases, or 10 per cent of the total, were either twenty years old or



CHARTS 7 AND 8.

less; seventy cases, or 35 per cent, were in the twenty-five-year age group; sixty-four cases, or 43 per cent, were in the thirty-year age group; and twenty-eight cases, or 14 per cent, were in the thirty-five-year age group. One hundred and eighty-two soldiers, or 91 per cent of the total, were in the twenty- to thirty-five-year range, and this would be expected to be the case in military service. The age of onset of the asthma occurred frequently in childhood, and decreased rather rapidly after the age of thirty.<sup>12</sup>

*Chart 4.*—It is of interest to note in this chart that of the total number of asthmatics 79 per cent, or 158 patients, had less than two and one-half

years of service prior to their final disposition in the Army; that 14 per cent, or twenty-eight patients, had up to four years' service; and that 7 per cent, or fourteen patients, had over four years' service. This observation indicates that asthmatic persons break down rather rapidly and require disposition by the end of two and one-half years.

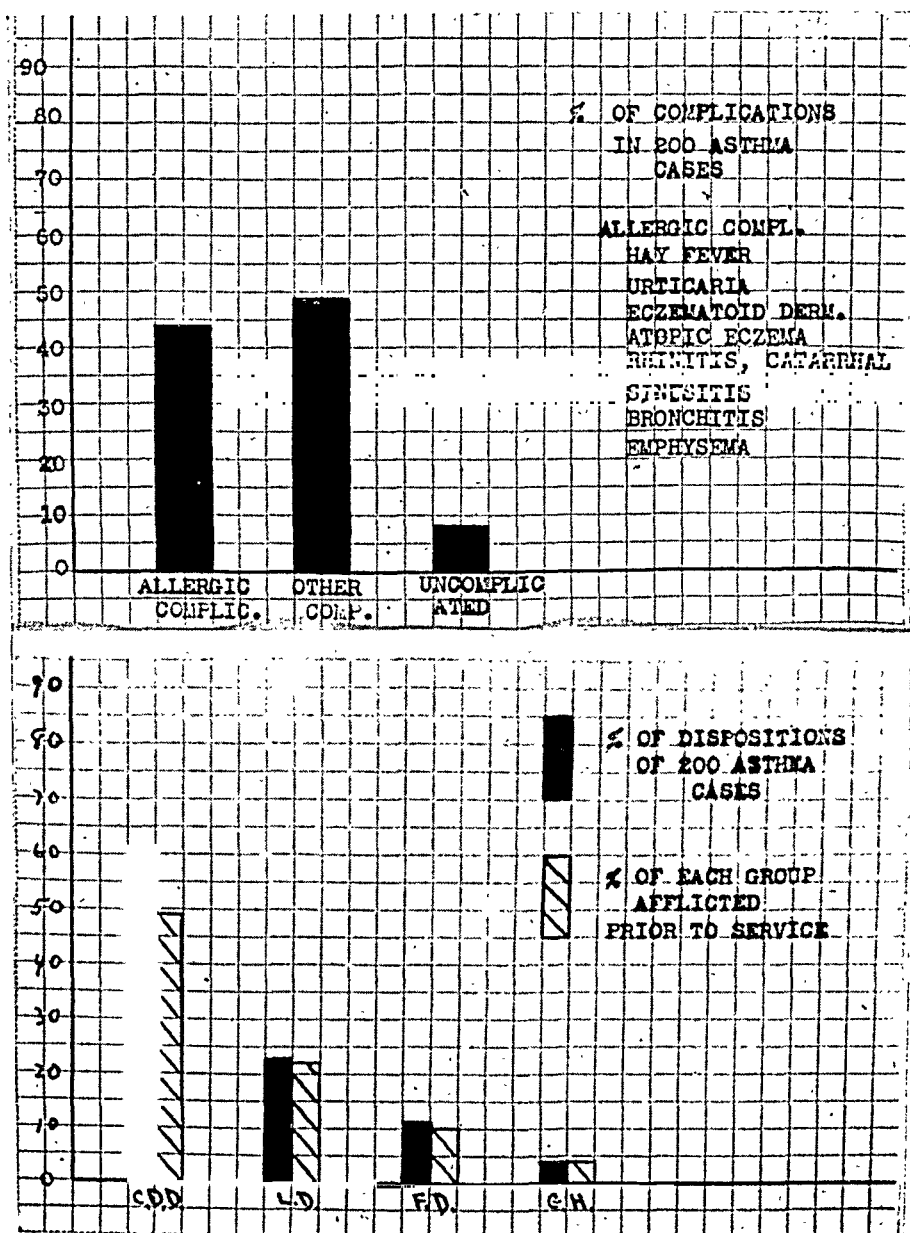
*Chart 5.*—In this chart we note that thirty cases had their initial attack of asthma in the service, and that 9 per cent of this group, or eighteen cases, had their first attack overseas. Of the total 200 cases, 48 per cent, or ninety-six patients, went overseas, and each soldier of this group was hospitalized overseas because of his asthma and required evacuation to the United States for study, treatment and final disposition.

*Chart 6.*—Although mobilization regulation MR 1-9<sup>11</sup> states that asthma of any degree is disqualifying for induction into the Army, 170 patients, or 85 per cent of this group, had the onset of their asthma prior to military service. Of the total group, thirty patients, or 15 per cent, had their initial attack of asthma incident to service, and seventy-eight cases, or 39 per cent, were aggravated by service, making a total of 108 patients, or 54 per cent, who had the onset or an aggravation of their asthma in the service.

*Chart 7.*—This chart reveals that the asthma was extrinsic in type in 140 cases, or 70 per cent; combined extrinsic and intrinsic in fifty-five cases, or 27.5 per cent; and intrinsic alone in five cases, or 2.5 per cent. These findings are in accord and conform to Table I of the classification described above.

*Chart 8.*—This chart shows that most of the extrinsic asthmatic soldiers were found to be skin sensitive to multiple inhalant allergens. Of the total, 166 cases, or 83 per cent, were sensitive to inhalants, including dust, feathers, molds, wool, cotton, kapok and tobacco. Of these patients, 112 were also sensitive to pollens, including both giant and dwarf ragweed, timothy, Bermuda grass, Johnson grass, redtop, orchard grass and careless weed. In addition, 154 of the patients, or 77 per cent, were sensitive to various food allergens, the most common being in the cereal, egg, milk and meat groups. The previous chart revealed the small number of purely intrinsic cases, and this group was sensitive by skin tests primarily to the upper respiratory bacteria.<sup>4</sup> The diagnosis of these cases was made largely by the history of repeated upper respiratory infections followed by asthmatic paroxysms. The combined extrinsic and intrinsic types were essentially a combination of the above, that is, they had positive skin tests and clinically verified sensitivity to inhalant and bacterial allergens. In some instances the extrinsic factor predominated, while in others the intrinsic factor predominated, with a greater or lesser degree of organic or functional complication.

*Chart 9.*—This chart and Table II present the associated allergies, complications and coexisting diseases included among these 200 soldiers. Of



CHARTS 9 AND 10.

the total, 184 patients, or 92 per cent, presented associated allergies, complications or coexisting diseases, and sixteen patients, or 8 per cent, were uncomplicated.

*Chart 10.*—The disposition of patients from a general hospital depends in a great measure on the requirements of the military service as well as on the physical condition of the soldiers. With the changing by the War Department of the physical requirements for limited duty, a number of asthmatics were discharged on a certificate of disability; however, when the manpower shortage became acute, some mild to moderate asthmatics were retained in service in limited duty capacities conforming to their physical abilities. Disposition was carefully evaluated for the 200 asth-

# BRONCHIAL ASTHMA—RUDOLPH

TABLE II. COEXISTING CONDITIONS

	Number	Per Cent
Hay fever .....	60	30.0
Sinusitis .....	18	9.0
Tonsillitis .....	17	8.5
Emphysema .....	14	7.0
Urticaria .....	10	5.0
Intestinal parasites .....	8	4.0
Catarrhal rhinitis.....	8	4.0
Bronchitis .....	7	3.5
Eczematoid dermatitis.....	7	3.5
Atopic eczema .....	6	3.0
Nasopharyngitis .....	5	2.5
Malaria .....	5	2.5
Dermatitis .....	4	2.0
Conjunctivitis .....	2	1.0
Polypi .....	2	1.0
Gastric ulcer .....	2	1.0
Adenopathy .....	1	0.5
Periostitis .....	1	0.5
Bronchiectasis .....	1	0.5
Hematuria .....	1	0.5
Lung abscess .....	1	0.5
Neuritis .....	1	0.5
Pleurisy .....	1	0.5
Psychoneurosis .....	1	0.5
Rheumatic fever.....	1	0.5
	184	92.0%

TABLE III. TWO HUNDRED ASTHMATIC CASES

AS A CIVILIAN:		
1. Times hospitalized for asthma.....	0	0
2. Months lost because of asthma.....	580	2.9
AS A SOLDIER:		
1. Number of hospital admissions.....	1180	5.9
a. For asthma .....	810	4
b. For other than asthma.....	370	1.9
TOTAL MONTHS LOST DUE TO ASTHMA WHILE IN THE ARMY .....	797	3.98
BEFORE LEAVING STATES:		
1. Times relieved from duty due to asthma.....	220	1.1
2. Times hospitalized for asthma.....	70	.35
3. Months lost due to asthma.....	157	.78
WHILE OVERSEAS:		
1. Times relieved from duty due to asthma.....	570	2.85
2. Times hospitalized for asthma.....	210	1
3. Months lost due to asthma.....	640	3.2
TOTAL SERVICE IN MONTHS.....	6040	30.2
MONTHS OVERSEAS SERVICE.....	2410	12.05
MONTHS SERVICE IN STATES.....	3630	18.15

matic patients. Of these, as shown in Chart 10, twenty-three patients, or 11.5 per cent, were returned to full duty; forty-seven patients, or 23.5 per cent, were returned to limited duty; eight patients, or 4 per cent, were transferred to veterans' hospitals; and 122 patients, or 61 per cent, were discharged on a certificate of disability. In view of the relative frequency of exacerbations or aggravations of symptoms on overseas duty, for those who were being returned to a limited duty status it was recommended that they be placed on duty within the continental limits of the United States. It would appear from the foregoing data that an asthmatic soldier as a rule does poorly in military service. He is frequently invalided, requires frequent hospitalizations, as is shown in Table III, and after a relatively short period of duty more than half of them must be separated from the service. Conclusions drawn by Alford<sup>1</sup> in a recent article on asthma are as follows:

## BRONCHIAL ASTHMA—RUDOLPH

1. "Men with active bronchial asthma should not be inducted into the Army.
2. "Soldiers with bronchial asthma may be placed on nonstrenuous duty if:
  - (a) Attacks are due to a single sensitivity for which rapid, adequate treatment is available;
  - (b) Attacks are mild or infrequent, not preventing light duty;
  - (c) The initial attack was overseas; and
  - (d) The attack in the Army was a recurrence from childhood."

An additional report by Leopold<sup>9</sup> on asthmatics returning from overseas indicates that the greatest majority of soldiers continue to have asthma after their return to the States. This was true in 95.5 per cent of his group, and of the total group 31.5 per cent had the initial onset of their asthma overseas, and 68.5 per cent had a recurrence or aggravation of a pre-existing asthma overseas. He considers hot and humid climates especially bad for asthma and believes that they were precipitating factors in his series of cases.

### TREATMENT

Soldiers having acute, isolated attacks brought about by intermittent exposure to excitants, perhaps precipitated by overexertion, emotional disturbances, acute infections or fatigue, respond well to vasoconstrictor drugs, since chronic pathologic changes have not had time to become established in the lungs. Ephedrine in  $\frac{3}{8}$  gr. doses given by mouth in capsules may be sufficient for relief. Phenobarbital will counteract the nervousness and insomnia often produced by ephedrine and should be added; however, in many cases the barbiturates produce an obscure, insidious increase in the asthmatic symptoms, which may be masked for a time by the action of ephedrine. Hence, it is well to test the asthmatic patient with a small initial dose of the barbiturate. An aqueous solution of epinephrine, 1:100, sprayed into the mouth through a special nebulizer and inhaled into the bronchial tree is effective when available, and we have found this to be of definite value in a number of our patients.

We have employed combinations of caffeine citrate, ephedrine sulfate and phenobarbital, one-half grain of each, with considerable benefit. Aminophylline, 1:5 to 3 gr. tablets, repeated every three to four hours by mouth is an active antispasmodic drug, and has been especially beneficial in the intrinsic cases. For severe paroxysms, epinephrine by parenteral injection is our ranking therapeutic agent. Small doses, 0.1 to 0.3 c.c. of the 1:1,000 solution, are usually effective. Although as large a dose as 0.6 c.c. may be necessary, we have found it better to give repeated small doses every thirty minutes (0.3 to 0.5 c.c.).

When the asthma has become chronic, infection of the continuously edematous bronchial mucosa adds to the constriction, giving rise to bronchitis, emphysema and atelectasis. Under these circumstances, in addition to remedies already mentioned, expectorants, particularly iodides, give relief by thinning the thick, tenacious bronchial secretion. The saturated aqueous solution of potassium or sodium iodide may be given orally, 5 to

30 minims in water after meals. Small amounts of codeine may be required to control coughing. Morphine must not be used for patients with chronic asthma, as it frequently increases symptoms.

For status asthmaticus, aminophylline should be given intravenously very slowly,  $3\frac{3}{4}$  to  $7\frac{1}{2}$  gr. diluted in 10 to 20 c.c. of saline.

Anoxia resulting from a prolonged attack is corrected by oxygen inhalations. Hypertonic solutions, such as 25 to 50 per cent glucose in amounts of 50 c.c. may be given intravenously to reduce bronchial edema.

All sources of continuous infection or irritation of the bronchial system, such as chronic sinusitis, must be given appropriate attention. Chronic infection of the pulmonary tissues, particularly bronchiectasis, if present, must be eradicated, if necessary, by surgical intervention. None of our patients required this treatment.

In all allergic soldiers multiple sensitization must be considered, as is indicated in the data. Drugs must therefore be used with caution, since the salicylates, coal-tar products, may aggravate an asthmatic tendency, or even precipitate an attack.

Belladonna, through its paralyzing effect upon bronchial nerve endings, may act to relax smooth muscle spasm, but at the same time it may dry the mucous surfaces and block the bronchi with thick mucus.

Calcium, histamine, histaminase, and potassium chloride alone have all been disappointing when tried for the relief of asthma, in this group of asthmatics.

#### CONCLUSION

The prognosis of bronchial asthma is notoriously uncertain. Asthma may manifest itself by a single attack, although this is unusual. It may continue for many years, or it may disappear only to recur years later. There are two significant facts regarding the prognosis of asthma, namely, that death during attacks is exceedingly rare, and the degree of disability is dependent largely upon the extent of the complications.

In the disposition of the allergic soldier, a board of medical officers has to consider the severity or constancy of the symptoms, the response to therapy, and the professional opinion of the attending medical officer. The ability of the patient with asthma and the degree of his incapacity have been seriously considered in all instances at this hospital. Reassignment would be advisable frequently if proper placement and allergic care could be continued. This type of disposition would of course be ideal, since both the soldier and the Army would profit mutually. However, in some cases the only correct procedure is to discharge the asthmatic soldier on a certificate of disability. The data presented above reveals no absolute standard which can be depended upon as to ultimate disposition. In the cases of bronchial asthma which we have discharged from the service we were governed in the main by the severity of symptoms and the fact that these symptoms were so severe that it was believed these men could no longer perform satisfactorily the duties required of a soldier in the Army.



When the physical manifestations of an allergic state have appeared, the offending substance must be discovered. If it is material that can be easily avoided, such as food that can be eliminated from the diet, the problem is simply solved. If the agent cannot be abolished, the affected soldier may be removed from the environment. This procedure is applicable only for the seasonal irritants, and this is not always possible in the Army. In many instances the asthmatic soldier may be successfully hyposensitized to the offending allergen, but here too the element of time does not always permit the complete fulfillment of this procedure, so that remedial measures must be employed in most instances.

## SUMMARY

1. Bronchial asthma, its related conditions and complications, is responsible for an enormous morbidity in the Army. This fact is revealed by a number of recent surveys in the literature and by the data on 200 cases of bronchial asthma reported in this paper.

2. For the purpose of clarity, the statistics in this report on the study of the asthmatic condition of each soldier was governed largely by the allergic concept and each case was evaluated on the basis of a generally accepted definition of asthma, a recognized classification, and acceptable specific criteria for the diagnosis of allergic asthma.

3. The statistical findings brought to light the following facts:

- (a) That 135 cases, or 67.5 per cent of the total of 200 cases, had a positive family history;
- (b) That the age range of the soldiers with asthma in 182 cases, or 90 per cent, was from twenty to thirty-five years;
- (c) That 158 cases, or 79 per cent, had less than two and one-half years' service prior to final disposition;
- (d) That 170 cases, or 85 per cent, had the onset of their asthma prior to military service, and only thirty cases, or 15 per cent, had their initial attack incident to service;
- (e) That 108 patients, or 54 per cent, had an overseas onset or aggravation of their symptoms;
- (f) That 184 cases, or 92 per cent, had associated allergies, complications or coexisting diseases; and finally
- (g) That 122 cases, or 61 per cent, were discharged on a certificate of disability; forty-seven cases, or 23.5 per cent, were returned to limited duty; twenty-three patients, or 11.5 per cent, were returned to full duty; and eight patients, or 4 per cent, were sent to veterans' hospitals.

4. In the cases of bronchial asthma which we have discharged from the service we were governed in the main by the severity of symptoms and the fact that these symptoms were so severe that it was believed that these men could no longer perform satisfactorily the duties required of a soldier in the Army.

*(Bibliography on Page 276)*

# CARCINOMA OF THE LUNG WITH ASTHMATIC SYMPTOMS

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THE diagnosis of asthma as a rule is quite simple. Patients often report to your office with the diagnosis already made by friends or relatives, but the diagnosis of asthma is not always that simple, for there are many things which may produce a wheeze. After all, a wheeze is only an indication of a mechanical interference with respiration. The presence of râles in the chest in conjunction with a history of asthma, is not in itself proof of bronchial asthma. It has been said, "all that wheezes is not asthma," and it is well to keep this fact in mind when making a simple diagnosis of bronchial asthma.

Of all those things which may produce a mechanical wheeze in the bronchi, carcinoma of the lung is responsible in a small percentage of cases. In a series of seventy-five bronchogenic carcinoma cases studied by Overholt and Rumel, 38 per cent gave symptoms of dyspnea or wheezing.<sup>2</sup> The purpose of this paper is not to point out the diagnostic features of lung carcinoma, but to emphasize the fact that some of these bronchogenic carcinomas may follow the pattern of bronchial asthma. Four cases will be presented to illustrate this point.

## CASE REPORTS

*Case 1.*—A man, aged fifty-two; chief complaint—asthma.

For fifteen years, this man had a nonproductive cough present both summer and winter. In May, 1936, this case was diagnosed as bronchial asthma, and a series of skin tests was made. A vaccine was prepared from the sputum, and he was treated for five months without benefit. A submucous resection was performed, and his teeth were removed.

While his complaint in the beginning was cough, he began to wheeze in January, 1937, and in May had his first acute attack of asthma. This attack lasted four days, and he was exceedingly short of breath and wheezed. Adrenalin was given and he coughed up bloody, gelatinous secretion. While this relieved the attack of asthma, the cough persisted.

He consulted another physician who made more vaccine. Adrenalin taken twice daily, controlled his wheezing, but did not control the coughing. His attacks of asthma became increasingly worse, and he lost forty pounds in weight. He became hoarse, and complained of substernal soreness.

He reported for consultation in November, 1937.

His family history was negative for allergy, and laboratory findings showed no eosinophils in the sputum. A few wheezing râles could be heard over the sternum, the apices were fairly clear, and breath sounds over the right midchest were difficult to elicit.

At the time he reported for consultation, no x-ray studies had ever been made of the chest, but when x-ray studies were made, the roentgenologist's report was as follows: "Diaphragms, heart, and mediastinum are within normal limits. The trachea is displaced to the right, indicative of some retraction of the right lung. The left lung fields appear fairly normal except for some slight increase in the vessel markings throughout, and evidence of some emphysema of the parenchyma.

## CARCINOMA OF THE LUNG—MOORE

On the right side there is a large increase in the right hilar shadow, extending into the right lower lobe, well out toward the periphery and down toward the diaphragm. There is very marked fibrosis in the region. It could be the result

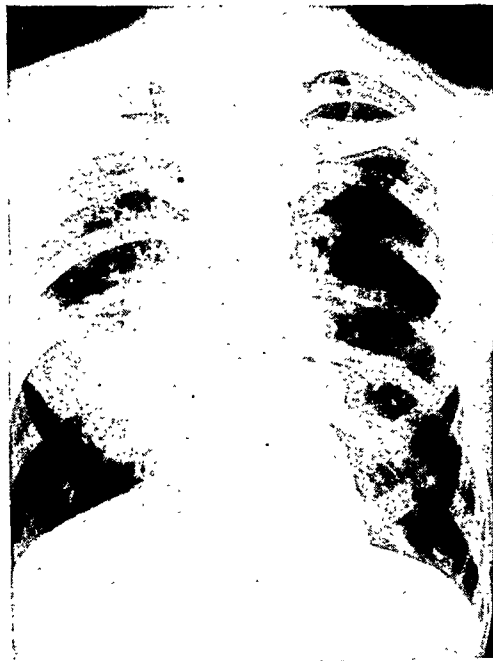


FIG. 1.

of either an old, healed abscess, or a neoplasm involving the bronchi in the region. It is probably the result of an old abscess which could be tuberculous." (Fig. 1).

Ten days later, this man died of pulmonary hemorrhage, and postmortem examination showed carcinoma of the right bronchus.

*Case 2.*—A woman, aged fifty-eight; chief complaint—asthma.

This patient could not fix the date when symptoms began, but believed that she experienced shortness of breath on exertion for the past four years. In 1938, a wheeze was noticed on exertion, and she consulted her physician who made a diagnosis of asthma, and recommended a change of climate. The wheezing gradually became worse, and shortness of breath persisted. One year later, she purchased an adrenalin spray, and this was used several times daily with help. Following the use of this spray, she would cough up a thick, yellowish secretion which gave relief. Later she coughed up blood-streaked sputum.

She reported for consultation in March, 1940.

Her family history and her own past history were negative for allergy, and there were no eosinophils in the sputum.

Wheezing râles were present in both respiratory phases, heard best over the midsternum, and atelectasis was suspected (Figs. 2 and 3).

The roentgenologist's report was as follows: "A very unusual, extensive, irregularly solid type of infiltration is shown extending into both lung fields. Some irregular annular zones of increased density are present which are bordered by hazy areas. The solid portions probably represent large metastatic nodes which produce atelectasis. Pleural changes are present at the bases which deform the costophrenic angle and sulci. No metastatic lesions are seen in the rib cage or the dorsal spine."



FIG. 2



FIG. 3



FIG. 4



FIG. 5

This patient died in June, 1940, and postmortem examination showed carcinoma of the lung.

*Case 3.*—A man, aged fifty-six; chief complaint—asthma.

This patient gave a history of asthma for the past three years. He wheezed, was short of breath, and had a productive cough. The wheezing was worse when lying down, and with exertion.

In October, 1942, a series of skin tests had been made, and he was placed on a very restricted diet. While he thought he was better on the diet, he lost fifty pounds in weight in five months. He was advised by his physician to discontinue the diet, change climates, and in February, 1943, he came to Portland.

He reported for consultation in February, 1943.



FIG. 6



FIG. 7

The family history was negative for allergy.

There was limited expansion on the left side, with dullness and distant breath sounds. Wheezing râles could be heard both anteriorly and posteriorly (Fig. 4).

The roentgenologist reported his findings as indicative of chronic pneumonitis, tuberculosis, or mycotic infection. Although the history and symptoms were somewhat suggestive of asthma, the findings suggested the possibility of bronchogenic carcinoma.

By June, 1943, he had lost sixty pounds, and was having chest pain. He noticed blood-streaked sputum, and complained of an obnoxious taste and odor to the sputum. Examination of the chest showed atelectasis of the left side, and x-ray findings at that time suggested strong indications of an extensive tuberculous involvement of the left lung (Fig. 5).

Bronchoscopic examination revealed a growth extending into the left main bronchus, biopsy of which proved it to be carcinomatous.

In July, 1943, the patient died.

*Case 4.*—A woman, aged fifty-six; chief complaint—asthma.

This patient's first attack of asthma followed a coronary disease in 1942. She was short of breath, and wheezed. One year later, a series of skin tests had been made, and vaccines administered without benefit.

She reported for consultation in May, 1944.

Her family history was negative for allergy.

There was a definite inspiratory wheeze, heard over the midchest. The x-ray studies showed typical fibrosis as seen in chronic asthma, but no well defined pathology in the chest. The vocal cords were examined and found to have a definite paralysis which did not open with inspiration, but appeared to have the reverse reaction and constricted during deep inspiration (Fig. 6).

X-ray examinations six months later showed marked retraction of the mediastinum to the left, and the trachea was markedly deviated. From the bronchoscopic examination one could see a stricture of the left bronchus (Fig. 7).

She became more dyspneic, the cough was productive, and sputum contained

## CARCINOMA OF THE LUNG—MOORE

mucopurulent material, but no blood. Substernal pains developed and she complained of constriction about her chest.

The final x-ray was taken in March, 1945, and the roentgenologist reported: Apices clear, increased markings of both lung fields. Mediastinum pulled to the left. Increased density of fifth interspace probably a metastatic lesion.

The patient had a sudden loss of weight and died in April, 1945.

The diagnosis was lung carcinoma.

These four patients did present definite symptoms of asthma, were diagnosed and treated as such, and some had relief with the use of asthmatic remedies. Carcinoma was not considered in the early phases because the symptoms were masked by the characteristic asthmatic wheeze. While some of these cases no doubt could have been diagnosed earlier if carefully examined, the diagnosis became evident as they progressed to their termination.

### *Carcinoma*

Usually no record of allergy in the past or family history.

Symptoms develop after forty-five years of age.

Cough precedes the wheeze by several months.

Wheezing râles localized.

Diaphragm arched.

No eosinophils in the sputum.

Blood often in the sputum.

Marked loss of weight and rapid downhill course.

### *Asthma*

History of allergy usually present.

Symptoms develop before forty-five years of age.

Cough usually comes with or follows the wheeze.

Wheezing râles generalized.

Diaphragm flattened.

Eosinophils present.

Blood seldom in the sputum.

Weight and course remain about the same.

Carcinoma of the lung may manifest itself in many ways, and the asthmatic syndrome is presented in a relatively large group of cases. Carcinomatous involvement of the lung is much more common than is usually believed. Some have reported as high as 18.5 per cent in all autopsies performed in one of the large general hospitals. In the Cleveland City Hospital, the lung is considered the second most frequent site of carcinoma, the stomach being the first.<sup>1</sup>

Carcinoma of the bronchus at first produces no symptoms or clinical signs, only a dry, irritating cough, but as the tumor increases in size, a segmental emphysema results. In this emphysematous stage, wheezing and asthmatic breathing make their appearance. Dyspnea and wheezing in the Overholt and Rumel series were found to be present in 38 per cent of bronchogenic carcinomas, and are considered early symptoms.<sup>2</sup>

It is in the stage of partial obstruction of the bronchus that one might make an erroneous diagnosis of asthma. Secretion which is produced adds to the asthmatic symptoms. As the tumor begins to break down, purulent sputum is noted, with occasional hemorrhages. In the last stage of atelectasis, the picture changes completely, and all symptoms of asthma then disappear.

Most cases of carcinoma of the lung are not diagnosed until it is too late for lobectomy. Surgeons have made great strides with encouraging

results, but if these patients are to be helped, we as allergists and internists must recognize symptoms early.

X-ray is often misleading in the early diagnosis of carcinoma of the lung. The clinical signs and history are far more important and all cases in which carcinoma is suspected should be bronchoscoped.

The differential diagnosis between allergic bronchial asthma and bronchogenic carcinoma is offered in the accompanying table:

## CONCLUSIONS

Bronchogenic carcinoma may assume the pattern of asthma especially in the stage of partial obstruction with segmental emphysema. Therefore, the wheeze should be an early symptom of bronchogenic carcinoma.

Four cases are presented to illustrate the importance of differentiating asthma from lung carcinoma and some differential diagnostic points are given.

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## The Study of Bronchial Asthma in a General Hospital

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## ALLERGY TO TOBACCO SMOKE

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DETAILED accounts of allergy to tobacco smoke are lacking in the medical literature. A. Brown records his observed incidence as one per cent of asthmatics due to tobacco or tobacco smoke. He does not differentiate between the two. Vaughan cites allergic episodes in several individuals, apparently precipitated by exposure to tobacco smoke. He also outlines briefly a procedure for making tobacco smoke extract.

In the present study, the records of 370 consecutive allergic patients seen in private practice were studied. No note was made as to whether they were smokers or nonsmokers. Thirty-five of this number, or between nine and ten per cent, gave a definite history of their respiratory allergy being precipitated or aggravated by tobacco smoke. In every case, the smoke was being generated by some other person or persons in the immediate vicinity. Out of these 370 patients, 229 had respiratory allergy. By respiratory allergy is meant hay fever, perennial or seasonal, and bronchial asthma, or asthmatic bronchitis, either or both, with or without accompanying allergic rhinitis.

Out of this entire group of patients, forty-seven, or approximately thirteen per cent, gave positive skin tests to tobacco smoke extract. The same tobacco smoke extract gave negative intracutaneous tests on ten non-allergic controls. There was a correlation of positive history with positive skin tests in nineteen.

From the foregoing, it is apparent that one may become sensitized to tobacco smoke alone, and furthermore that it should be considered an important factor in all respiratory allergy. With this in view, the following studies were carried out in an effort to establish tobacco smoke sensitivity as a distinct allergic entity.

### PROCEDURE

STEP I—Blood serum was obtained from an individual giving a positive history of allergy to tobacco, as well as a "4 plus" positive endermal skin reaction to tobacco extract. This serum was diluted with an equal volume of physiological saline, containing four-tenths per cent phenol. With this material, tobacco-sensitized passive transfer sites were made on three nonallergic subjects by introducing 0.10 c.c. intracutaneously. These tobacco-sensitized sites were exhausted with tobacco extract, used in routine skin testing, as follows: 0.05 c.c. of tobacco extract used in routine endermal skin testing was introduced endermally into the transfer sites. This was done every forty-eight hours until the resulting skin reactions became negative, as illustrated in Figure 1. All simultaneous control tests to the same tobacco extract were negative.



STEP II—Approximately 144 hours following the completion of Step I, tobacco-sensitized sites were again made on the same three nonallergic subjects, using tobacco-sensitized serum from the same batch. Attempts were made to exhaust these tobacco-sensitized sites with tobacco smoke

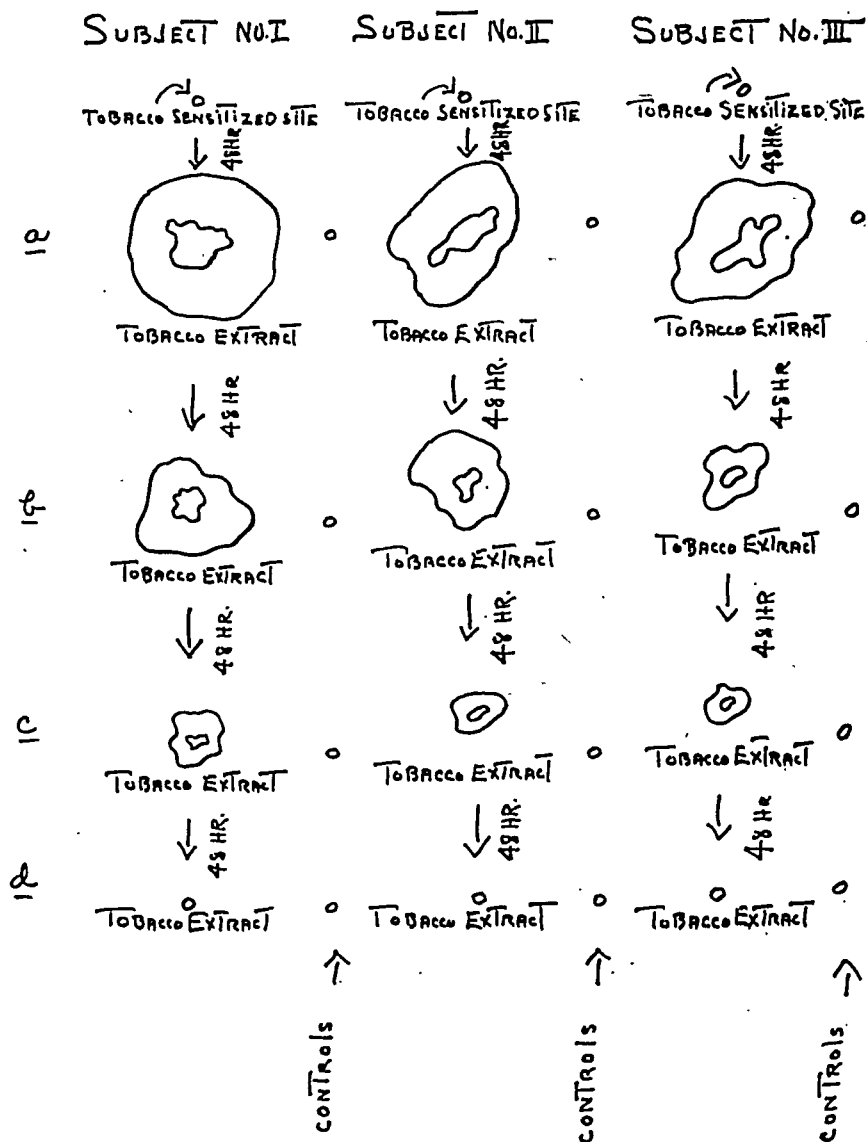


Fig. 1. Tobacco-sensitized passive transfer sites exhausted with tobacco extract.

extract, as follows: 0.05 c.c. of tobacco smoke extract used in routine endermal skin testing was introduced into each of these tobacco-sensitized sites. This was repeated every forty-eight hours until the resulting reactions were negative. Forty-eight hours after the tobacco smoke extract reacted negatively in the three tobacco-sensitized sites, 0.05 c.c. of the tobacco extract used in Step I was introduced into each site. This re-

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sulted in positive skin reactions, as illustrated in Figure 2. However, these reactions were reduced in size about 30 to 40 per cent, as compared with the unexhausted reactions in Figure 1. (Compare *a* in Fig. 1 to *d* and *e* in Fig. 2.)

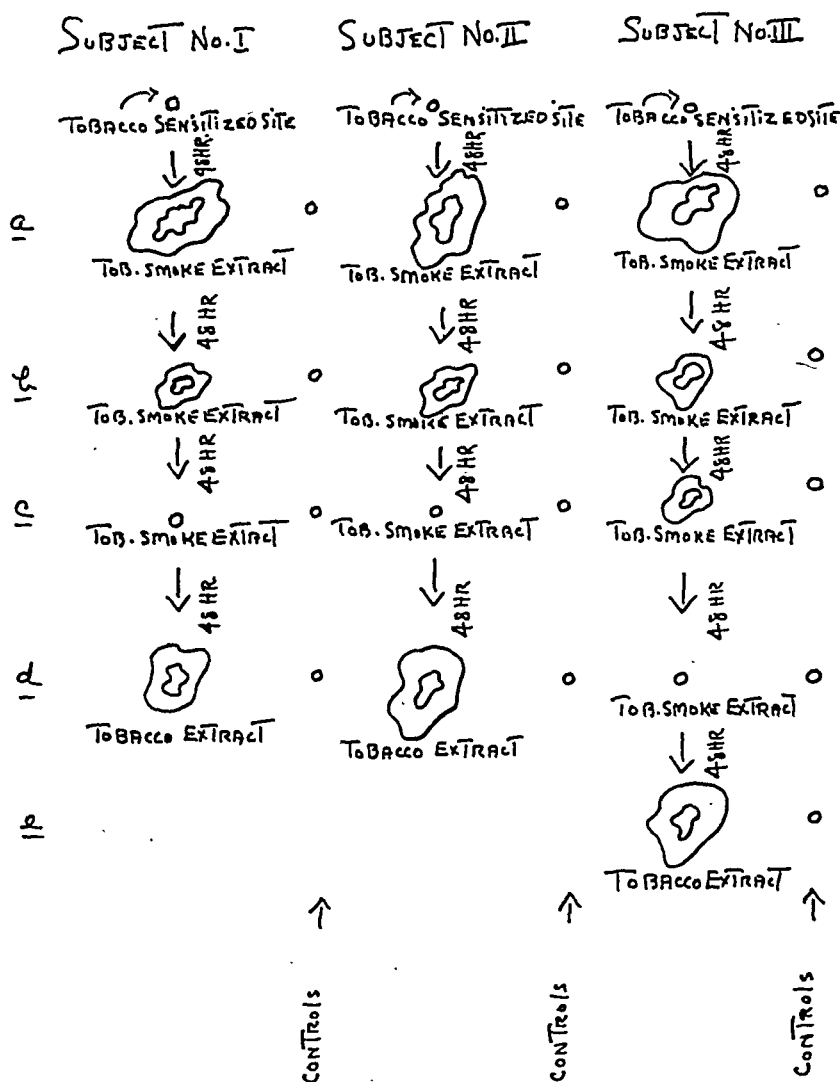


Fig. 2. Tobacco-sensitized passive transfer sites reduced with tobacco smoke extract (compare *d* and *e* in Fig. 2 with *a* in Fig. 1).

**STEP III**—Approximately two weeks following the completion of Step II, blood serum was obtained from an individual giving a positive history of allergy to tobacco smoke and a “4 plus” positive endermal skin reaction to tobacco smoke extract. This serum was diluted with an equal volume of physiological saline, containing four-tenths per cent phenol. With this material, tobacco smoke-sensitized passive transfer sites were made on three nonallergic subjects by introducing 0.10 c.c. intracutaneously. These

tobacco smoke-sensitized sites were exhausted with tobacco smoke extract used in routine endermal skin testing, as follows: 0.05 c.c. of tobacco smoke extract used in routine skin testing was introduced endermally into the transfer sites. This was done every forty-eight hours until the result-

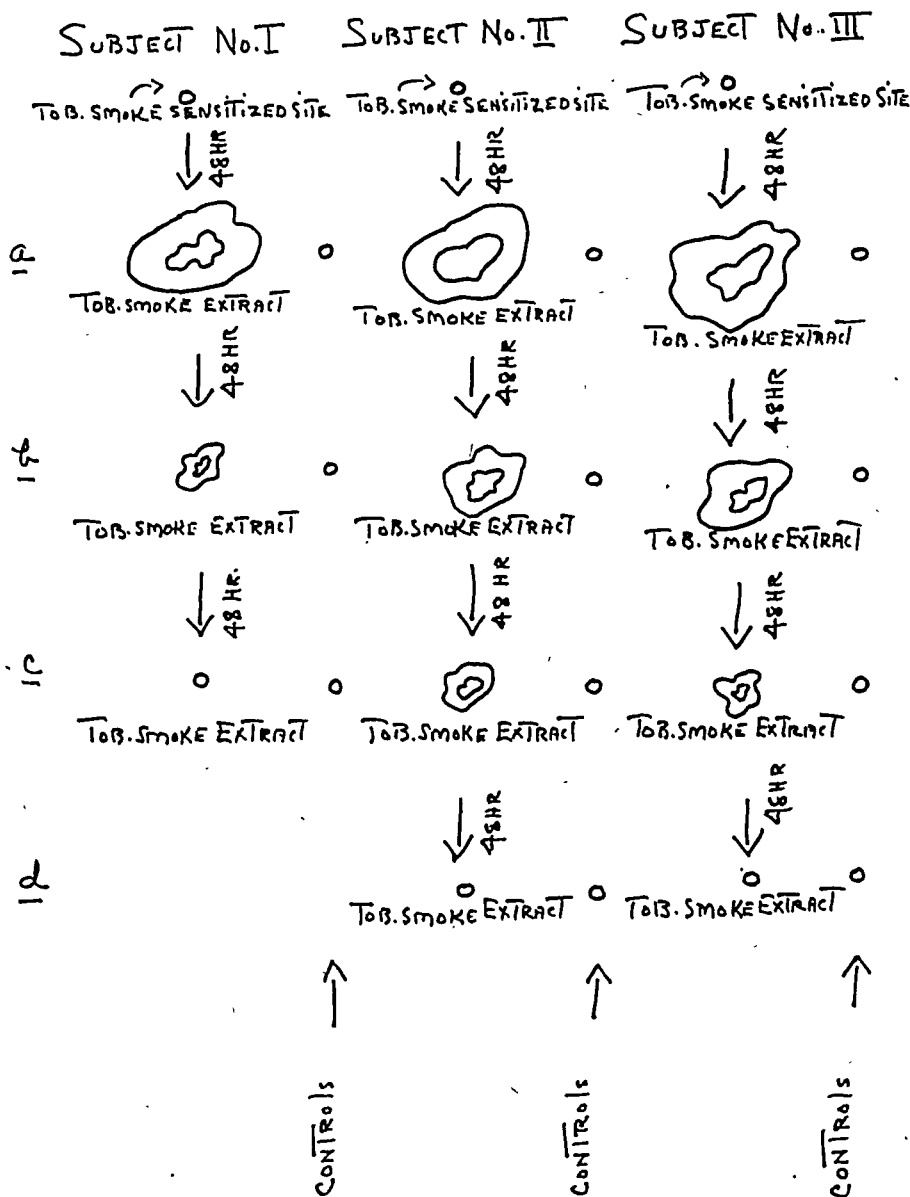


Fig. 3. Tobacco smoke-sensitized passive transfer sites exhausted with tobacco smoke extract.

ing skin reactions became negative, as illustrated in Figure 3. All simultaneous control tests to the same tobacco smoke extract were negative.

STEP IV—Approximately 144 hours following the completion of Step III, tobacco smoke-sensitized sites were again made on the same three nonallergic subjects, using tobacco smoke-sensitized serum from the same

batch. Attempts were made to exhaust these sites with tobacco extract, as follows: 0.05 c.c. of tobacco extract used in routine endermal skin testing was introduced into each of these tobacco smoke-sensitized sites. This was repeated every forty-eight hours, until the resulting reactions were nega-

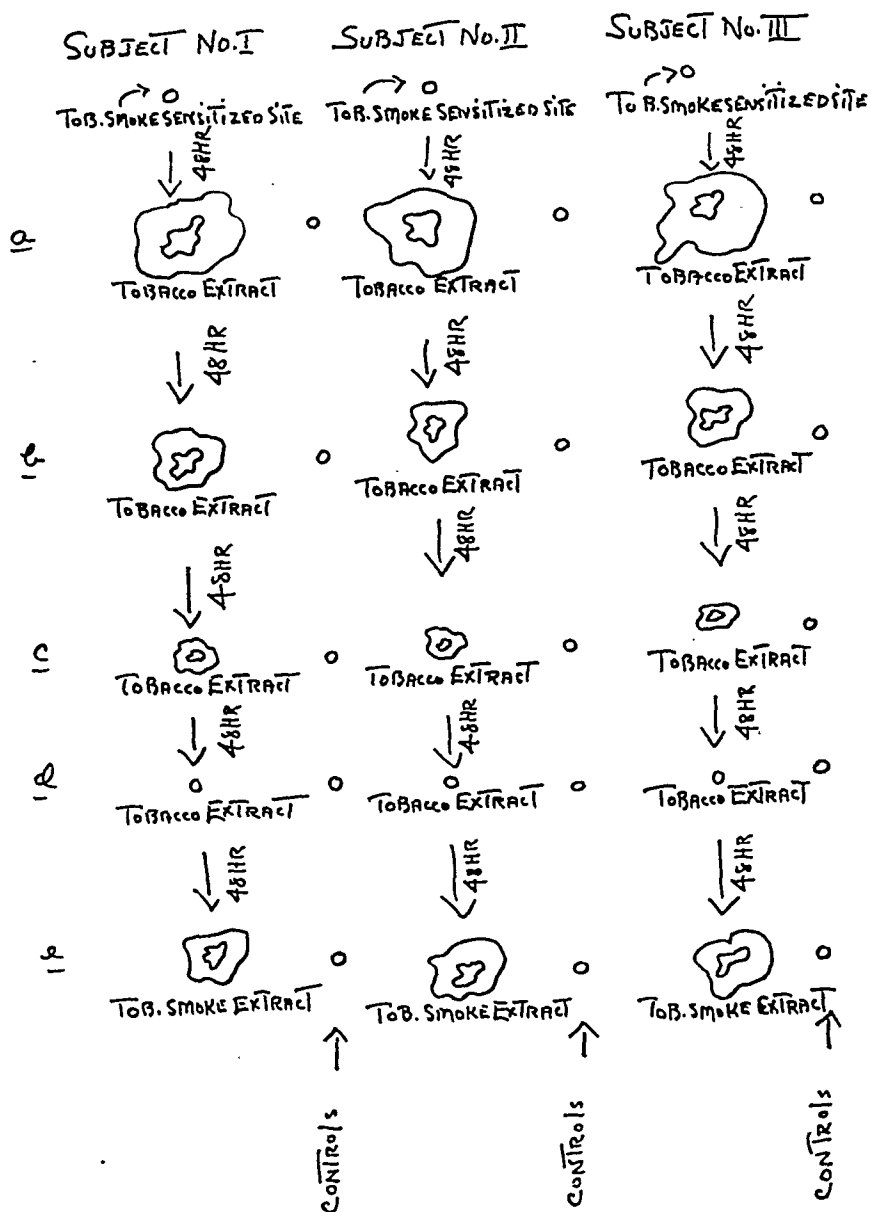


Fig. 4. Tobacco smoke-sensitized passive transfer sites reduced with tobacco extract (compare c in Fig. 4 with a in Fig. 3).

tive. Forty-eight hours after the tobacco extract reacted negatively in the three tobacco smoke-sensitized sites, 0.05 c.c. of the tobacco smoke extract used in Step III was introduced into each site. This resulted in positive skin reactions, as illustrated in Figure 4. However, these reactions were

reduced about 40 to 50 per cent as compared with the unexhausted reactions in Figure 3. (Compare *a* in Fig. 3 to *e* in Fig. 4.)

## SUMMARY

The records of 370 consecutive allergic patients seen in private practice were examined, showing that 9 or 10 per cent gave a definite history of their respiratory allergy being precipitated or aggravated by exposure to tobacco smoke. Approximately 13 per cent of this entire group gave positive skin tests to tobacco smoke extract. This same tobacco smoke extract gave negative intracutaneous tests on ten nonallergic controls.

Passive transfer sites of tobacco-sensitized serum were exhausted with tobacco extract. Passive transfer sites of tobacco-sensitized serum could not be completely exhausted, but were reduced approximately 30 to 40 per cent with tobacco smoke extract.

Passive transfer sites of tobacco smoke-sensitized serum were exhausted with tobacco smoke extract. Passive transfer sites of tobacco smoke-sensitized serum could not be completely exhausted, but were reduced approximately 40 to 50 per cent with tobacco extract.

## CONCLUSIONS

1. It is indicated from this study that allergy to tobacco smoke may be a distinct entity, exclusive of allergy to tobacco.

2. It may be further inferred that allergy to tobacco smoke cannot be adequately controlled by hyposensitization with tobacco extract alone.

3. It would probably be well to use both tobacco and tobacco smoke extracts in the course of routine skin testing.

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## ATMOSPHERIC POLLEN SURVEYS IN BRAZIL

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UNTIL 1941 a report is not to be found in the literature dealing with pollen counts in Brazil. The first paper on this subject was published in 1942 by Greco, Oliveira Lima and Tupinambá<sup>8</sup>, in which they give the results of their investigations on the pollen content of the air in Belo Horizonte, an inland city, about 200 miles northwest of Rio de Janeiro. This year round investigation revealed only one pollen season, that of the grasses, which occurs from mid-May to mid-June. The maximum count was 162 grains of grass pollen per 1.8 square centimeters. Pollens of other plant species were seen on the slides, but in a negligible number and sporadically, without defining a season. This study was carried out under standard conditions, i.e., the slides were exposed daily for twenty-four hours under a protective shelter, at about 8 meters above the ground, from 8 a.m. to 8 a.m., and the count expressed in grains per unit area of 1.8 square centimeters.

After completing this study, Oliveira Lima and the author became interested in knowing the atmospheric pollen situation of other localities of Brazil. They secured the co-operation of several colleagues, also interested in the problem, who were instructed to follow the standard method mentioned here in order to make the slide exposures in their own cities. Boxes holding the slides, especially devised by Oliveira Lima and Greco<sup>12</sup> and coated with glycerin jelly and methyl green, were sent to them. After exposure, the boxes containing the slides were returned to Belo Horizonte where the counting was made by Oliveira Lima and the author. In this way it was possible to cover a large number of localities and obtain data on the pollen content of the air in different sections of Brazil.

In this paper the data secured up to the present writing are summarized.

Daily pollen counts of the air of Rio de Janeiro were made from May, 1941, to July, 1942.<sup>7</sup> In this investigation, it was found also that there was only one season (grass) occurring from mid-May to mid-June. The highest number of pollen grains counted was 58, considerably lower than that of Belo Horizonte. In 1944 Oliveira Lima and co-workers<sup>11</sup> repeated the quantitative pollen studies of the air of Rio de Janeiro. Their findings were found comparable to those of 1941 and 1942.

Oliveira Lima and Greco<sup>13</sup> reported the pollen counts of the atmosphere of Belo Horizonte made during three consecutive years, i.e., 1940, 1941 and 1942. This study showed that, in spite of the variation in the amount of pollen caught from year to year, the season reoccurs at about the same time annually. The 1940 season occurred from the third week of May to the second week of June; in 1941, from May 14 to June 8, and that of 1942 from May 23 to June 15. The highest pollen counts were obtained in 1941; the second highest in 1940; and the lowest in 1942.

Oliveira Lima, Greco and Aguiar<sup>14</sup> made pollen counts of the city of Juiz de Fora (State of Minas Gerais) during the months of May and June. They found a definite grass season extending from May 22 to June 18. Pollen grains of other species were also seen on the slides, but in minute quantity and without seasonal delineation.

A study<sup>16</sup> of the atmospheric pollen content of Campinas (State of São Paulo) shows that this city has a grass season of three weeks' duration beginning in the fourth week of May. The highest count was 100 grains.

The quantitative pollen study of the atmosphere of Varginha (State of Minas Gerais) disclosed a grass season beginning on May 24, reaching a maximum of 100 grains on June 4 and ending June 18.<sup>18</sup> This observation was conducted daily from April to July.

The city of Barbacena (State of Minas Gerais) has a grass season extending from May 28 to June 24.<sup>15</sup> This is the longest season so far observed in Brazil.

Oliveira Lima, Greco and Lula<sup>17</sup> made daily pollen counts of slides exposed in the city of Salvador (State of Bahia), from March to August, 1942. This six-month investigation did not show any pollen season. The highest count was 5 granules per unit area of 1.8 square centimeters.

Greco and Oliveira Lima<sup>6</sup> conducted pollen studies in Dolores do Indaia and Abaeté, both in the state of Minas Gerais, during the months of May and June, 1942. They state that both cities have a grass pollen season of about three weeks' duration.

More recently, 1944, Greco and Pereira<sup>9</sup> carried on a pollen study of the atmosphere of Goiania (State of Goiaz). The observation was made daily from May to July, but did not disclose the grass season which has been found in other sections of the county.

According to Greco and Silva Junior<sup>10</sup>, in their report of the pollen content of the air of Ribeirão Preto (State of São Paulo), this city shows a grass season of three weeks' duration (May 19 to June 9) with high numbers of pollen grains on the standard slide area (up to 226). Here the observation was made daily from May to August.

According to Greco<sup>1</sup> the cities of Januária and Montes Claros, both in the northern part of Minas Gerais, do not have a grass season in the months of May and June.

Greco and Gabriel Diniz<sup>5</sup> investigated the pollen situation of the atmosphere of Curvelo (State of Minas Gerais). They state that this city presents a grass season of 21 days' duration, but of low pollen concentration. The highest count here was 52 grains.

Greco and França Junior<sup>4</sup> report the result of their study of the pollen content of the air of Serro (State of Minas Gerais) which was done from May to August. They found a grass season which lasted from May 30 to June 19 with a maximum concentration of 108 granules.

Greco and Bastos<sup>3</sup> made daily pollen counts of the air of Santos (State of São Paulo), from June 1 to September 7. This study is not altogether

## POLLEN SURVEYS IN BRAZIL—GRECO

enlightening because it was begun after the expected starting of the grass season. However, they report that a low grass pollen concentration was found up to June 12. After this date no other pollen was seen on the slides in sufficient number to individualize a season.



Fig. 1. All cities with grass season so far found in Brazil are located within square shown in map.

In 1944 Greco<sup>2</sup> studied the pollen concentration of Belo Horizonte (state capital of Minas Gerais), exposing slides in three different sections of the city: in the business center and in two residential districts at opposite ends of the town. The highest grass pollen count was obtained on the slides exposed in the east district with 400 grains of grass pollen on June 7; the second highest was that of the business center with a maximum of 96; the lowest was observed in the west district with a maximum of 89. The season started on May 21 and ended on June 17, according to the records for the business center of the city. For the residential sections the dates were roughly the same.

Oliveira Lima<sup>11</sup> has been conducting an investigation of the pollen situation of selected cities of the northern and southern parts of Brazil. His report will be of great value to the understanding of the problem.

### COMMENT

Though there is a large variety of species of grasses in Brazil, it seems safe to consider the *Melinis minutiflora* (known in Brazil as *Capim gordura* or *Capim melado*) as the chief source of the pollens caught on the



slides during the grass seasons above mentioned, because they coincide with the pollination of this species, and no grass season has been found to occur in sections of the country where *Melinis minutiflora* is not prevalent. Previously it was supposed<sup>8</sup> that *Cynodon dactylon* might be important, but more recently it has been observed that this grass is not as abundant as *M. minutiflora* and its flowering does not coincide with the highest pollen counts.

The only cities so far encountered with a grass season are located within a square roughly limited by 18° to 24° lat. south by 42° to 49° long. west (Fig. 1).

Though definite grass seasons have been disclosed in several cities of the country, the rarity of pollinosis among the Brazilian people is puzzling to the allergists of the country. Cases of asthma, perennial rhinitis, atopic eczema, etc., are almost as frequent there as they are in the United States, but those of hay fever are seldom encountered. The problem of hay fever in Brazil will be reported later.

#### SUMMARY

Atmospheric pollen counts are reported from the following 16 cities of Brazil, listed by states: *the capital*, Rio de Janeiro; *Minas Gerais*, Belo Horizonte, Juiz de Fora, Varginha, Barbacena, Dolores do Indaiá, Abaeté, Januária, Montes Claros, Curvelo, Serro; *São Paulo*, Campinas, Ribeirão Preto, Santos; *Baía*, Salvador; *Goias*, Goiania. In all except Januária, Montes Claros, Salvador and Goiania, was found a well-defined grass hay-fever season extending from mid May to mid June. This is caused principally by the pollen of *Melinis minutiflora* (*Capim gordura* or *C. melando*) and to a lesser extent that of *Cynodon dactylon*.

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(References continued on Page 328)

## EXPERIMENTAL APPROACH TO ORAL TREATMENT OF FOOD ALLERGY

### III. Oral De-allergization with Food Propeptans of Orally Allergized Animals

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THE great majority of individuals who present any kind of manifestation of food allergy have acquired their allergy by the enteral route. Moreover, the various symptoms of an underlying food hypersensitiveness are—almost exclusively—elicited by ingestion of the food in question. For many years, the senior author<sup>8</sup> has pointed to the fact that the oral administration of food digests—the so-called food propeptans\*—can at first temporarily inhibit a given food allergy, and then ultimately cure the condition completely.

The present paper is concerned with an investigation of this question along lines of animal experimentation.

Animals were allergized *orally* by means of food extracts; the allergic symptoms were elicited by *oral* administration of food extracts, and these very symptoms were inhibited by means of food propeptans, given *orally*. Similar experimental work with propeptans has been reported by Hamamoto.<sup>4</sup> These results would seem to constitute experimental confirmation of the therapeutic significance of specific food digests.

It is relatively easy to achieve experimental allergization by way of the mouth. Thus, guinea pigs can be allergized by oral administration of substances to which they are not accustomed—e.g. horse serum (Rosenau and Anderson, Aurichio, Hettwer and Kriz), milk (Vaughan), egg (La Roche, Richet and Saint Girons), and so on.

However, this does not occur in anything like the high incidence of shock that follows intravenous injection of the antigen. Thus, as Ratner<sup>7</sup> has reported, three out of forty-four orally allergized animals presented violent anaphylactic reaction to 5 c.c. of skimmed milk by mouth, while eleven of this series responded with moderate anaphylaxis to the same dose; and the remaining thirty animals presented little, if any, reaction. On the other hand, 50 per cent responded to milk, injected intravenously, with anaphylactic shock. Also, Hamamoto<sup>3</sup> found that only few of his

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\*Food propeptans are food digests derived from the individual foods through prolonged digestion with hydrochloric acid and pepsin, followed by some slight additional digestion with trypsin. Thus, these preparations contain all the protein cleavage products, chiefly proteoses but also peptones, sub-peptones, simple peptides and amino acids but not any native proteins (Urbach, Jaggard and Crisman.<sup>11</sup>) However, for reasons stated elsewhere in this paper, glycyrrhiza is added to the propeptans intended for therapeutic use. This saponin contains 1.4 per cent protein nitrogen. Pure food propeptans for analytic or experimental purposes will be supplied by Dalare Associates, 2300 Locust Street, Philadelphia 3, Pa., on request.

TABLE I. EFFECT OF ADDITION OF GLYCYRRHIZA ON DEGREE OF ENTERAL ALLERGIZATION OF GUINEA PIGS

Enteral Allergization*	Interval	Concentration of Allergen†	Clinical Manifestations
Egg white alone	2 weeks after last previous ingestion	1:10,000	Fatal anaphylactic shock
		1:100,000	Slight pruritus
		1:10,000,000	No symptoms
Egg white + 0.1 gm. of glycyrrhiza each day		1:100,000	Fatal shock
		1:10,000,000	Fatal shock

\*Feeding of 0.1 gm. of egg white for seven days.

†Dilution of egg white necessary to elicit anaphylactic shock in 1 c.c. doses, intravenously.

experimental animals, which had been orally allergized to milk, died from fatal shock when milk feeding was repeated after a two weeks' interval.

In order to achieve oral allergization in a higher percentage of instances, as reported above, irritation of the gastro-intestinal tract, e.g. by means of alcohol, may be tried (Hajos<sup>2</sup>). Furthermore, the degree of resorption can be greatly increased by removing the protective layers of mucus covering the mucous lining of the small intestine, e.g. by means of ox gall. Arloing, Langeron and Spassitch<sup>1</sup> claim that in this manner, they have succeeded in allergizing guinea pigs to antipyrine, quinine and olive oil. However, since animals do not readily tolerate ox gall, Urbach<sup>9</sup> augmented the allergizing properties of food antigens by adding the saponin glycyrrhiza which serves to increase resorption by dissolving the mucus of the small intestine (Table I). With the use of glycyrrhiza he even succeeded in allergizing guinea pigs orally to food digests.

#### ORIGINAL EXPERIMENTS

Fifty virgin guinea pigs, weighing approximately 250 grams, were allergized by oral administration of 2.5 c.c. of liquid egg white+0.2 grams of glycyrrhiza for seven consecutive days. And, as an alternative, another fifty animals were given 1 c.c. of 25 per cent alcohol solution followed immediately by 2.5 c.c. of liquid egg white.

These orally sensitized animals were highly sensitive three weeks after the last feeding, as shown by the fact that they responded with fatal anaphylactic shock to *intravenous* injection of 0.25 c.c. of 0.1 per cent liquid egg white.

#### Experiment 1

Guinea pig 720, sensitized to egg white by oral administration of 1.0 c.c. of 25 per cent alcohol solution followed immediately by 2.5 c.c. of liquid egg white daily for seven days.

Three weeks later the following procedure was carried out:

Treatment: None.

Shock Dose: Intravenous injection of 0.25 c.c. of 0.1 per cent liquid egg white.

Symptoms: Immediately fatal anaphylactic shock.

Schultz-Dale Test: Negative.

Lung Perfusion Test: Maximally positive

Similar but, in general, less dramatic reactions are caused if the shock dose is given by mouth. Thus, when an animal which had been sensitized orally was given the shock dose (7.5 c.c. of liquid egg white) by mouth,

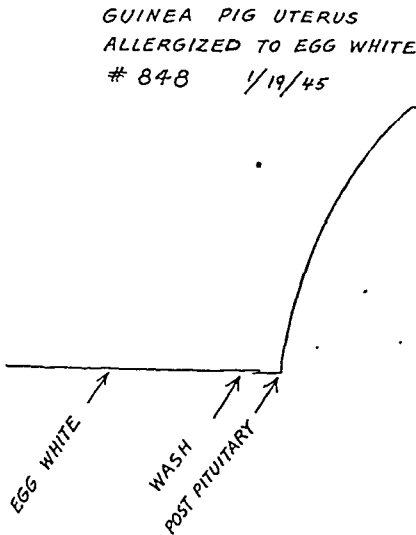


Fig. 1. Schultz-Dale test performed upon the uterus of guinea pig No. 848, allergized to egg white by the oral route, and killed two hours after the oral administration of a shock dose of egg white. There was no reaction upon the addition of egg white, indicating the absence of antibodies for native (unaltered) egg white. A final addition of posterior pituitary extract was made as a check upon the sensitivity of the uterus.

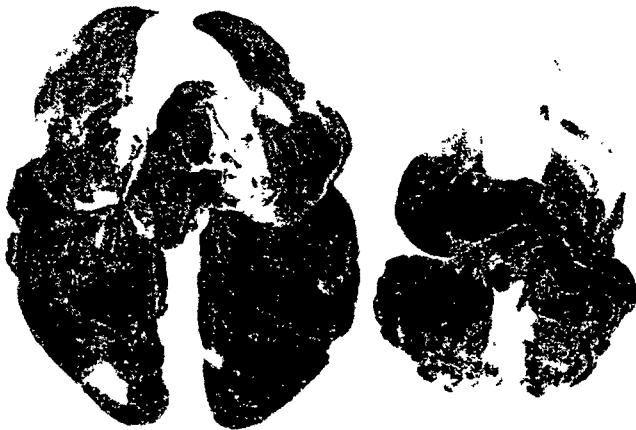
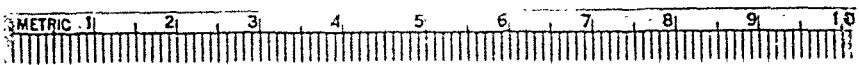


Fig. 2. Lung perfusion test performed upon the lung of guinea pig No. 848, allergized to egg white by the oral route and killed two hours after the oral administration of a shock dose of egg white. The lung (left) showed maximal inflation, indicating that the lung tissue is highly allergized. A control lung of a nonallergized animal of the same weight (right) showed a negative reaction in the lung perfusion test.

it presented, after five minutes or so, mild but definite allergic manifestations as evidenced by bristling, coughing and gasping respiration. These symptoms disappeared within half an hour. In two instances the guinea

pigs died in acute anaphylactic shock. Again the Schultz-Dale test was negative and the lung perfusion test brought on maximal inflation of the lung.

### Experiment 2

Guinea pig No. 848, sensitized to egg white by oral administration of 1.0 c.c. of 25 per cent alcohol solution followed immediately by 2.5 c.c. of liquid egg white daily for seven days.

Three weeks later the following procedure was carried out:

Treatment: None.

Shock Dose: Oral administration of 7.5 c.c. of liquid egg white.

Symptoms: Approximately five minutes after the shock dose the animal bristled, coughed and gasped deeply. The guinea pig recovered in half an hour.

Animal killed two hours after the oral shock dose.

Schultz-Dale Test: Negative (Fig. 1).

Lung Perfusion Test: Maximally positive (Fig. 2).

In contradistinction to *orally* sensitized animals, *parenterally* allergized guinea pigs will consistently exhibit both positive Schultz-Dale reactions and positive lung perfusion tests (Urbach, Jaggard and Crisman<sup>12</sup>).

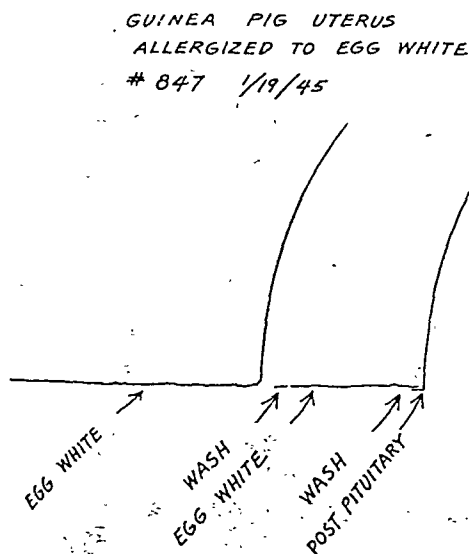


Fig. 3. Schultz-Dale test performed upon the uterus of a guinea pig, No. 847, allergized to egg white parenterally and killed two hours after the oral administration of a shock dose of egg white. There was a violent reaction following the addition of egg white, indicating the presence of considerable quantities of antibodies for egg white. No reaction followed a second addition of egg white, proving that the preceding one was specific. A final addition of post-pituitary extract was made as a check upon the sensitivity of the uterus.

### Experiment 3

Guinea pig No. 847, allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline.

Three weeks later the following procedure was instituted.

Treatment: None.

Shock Dose: Oral administration of 7.5 c.c. of liquid egg white.

Reaction: Bristling and coughing in about five minutes followed by severe gasping respiration for about one hour, after which the guinea pig recovered.

Animal killed two hours after the shock dose.

Lung Perfusion Test: Positive (Fig. 3).

Schultz-Dale Test: Positive (Fig. 4).

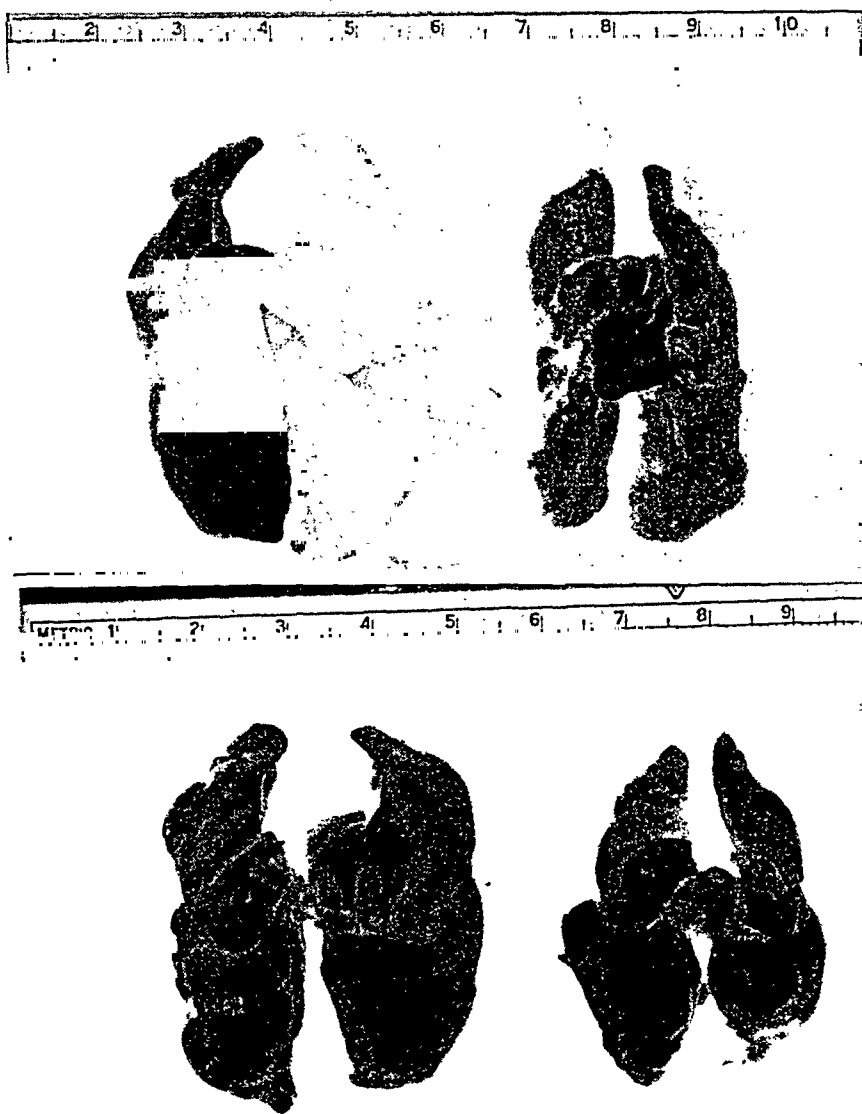


Fig. 4 (*above*)  
Fig. 5 (*below*)

Figs. 4, 5, 6 and 7. Lung perfusion test of animals in different states of de-allergization.

Guinea pigs are allergized to egg white by daily oral administration for seven consecutive days.

Three weeks following oral administration of egg white, guinea pig No. 847 (Fig. 4) exhibited a maximal positive reaction to egg white in the lung perfusion test. Guinea pig No. 775 (Fig. 5), treated with a series of *intravenous* injections of egg propeptan in increasing doses, received an oral shock dose of egg white. The lung perfusion test was less marked but definitely positive. Guinea pig No. 724 (Fig. 6) received one *oral* treatment with egg propeptan, followed by an oral shock dose of egg white. The lung was slightly but definitely positive. Guinea pig No. 749 (Fig. 7) received *oral* treatment with egg propeptan on *four consecutive days* always followed by an oral shock dose of egg white. Lung perfusion test was persistently negative.

Control lungs of nonallergized animals of same weight (*right*) show negative reactions in lung perfusion tests.

Fig. 6 (*above*)Fig. 7. (*below*).

How can one explain the most unusual fact that the uterus of animals, highly sensitized by the oral route, do not react to the addition of the specific antigen while the lung in the Manwaring-Kusama<sup>6</sup> test presents a maximal emphysema and animals of this series die instantaneously when the very same antigen is intravenously injected in very small amounts? There is not the slightest doubt that the Schultz-Dale test constitutes the most reliable and sensitive method for determination of sensitization of laboratory animals on one hand, and for the specificity of antigens, on the other. Yet, the high specificity of the Schultz-Dale is precisely the flaw which makes this procedure less useful for certain biologic and immunologic purposes than the anaphylactic or the skeptophylactic experi-

ments performed in living animals (Urbach and Wolfram<sup>13</sup>). This is because the Schultz-Dale method is so extremely specific that a positive reaction can be evoked only if the antigens used in the sensitization of the animal and in its reinjection are absolutely chemically identical. However, when antigens are immunologically related as to type-specificity but are not chemically identical they cannot produce a uterine reaction. The immunologic relationship which exists between a native protein and its digestion products (proteoses and peptones) and for which the term type-specificity is used, cannot be demonstrated by means of the Schultz-Dale test, but can readily be shown by less specific biologic methods such as the lung perfusion test and the anaphylactic experiment on the living animal.

When egg white is given orally, it is subjected to degradation both in the stomach and in the small intestine. The degradation products, especially the proteoses, are partly resorbed as such if the gastro-intestinal tract has been previously irritated by alcohol, or its resorptive capacity increased by glycyrrhiza, instilled in the stomach. This means that animals so prepared are sensitized not to native egg white but to proteoses of egg white. The reason that addition of native egg white to the sensitized uterus evokes no reaction is that the uterine muscle is unable to respond to the proteoses which, while they are immunologically related to egg white, are, however, chemically not identical with it. On the other hand, the lung perfusion test and the anaphylactic experiment are less specific and will react therefore to type-specific antigens (proteoses and the protein from which it is derived) although they are not chemically identical.

The same negative results are obtained as in orally sensitized animals, when one attempts to perform a Schultz-Dale test with egg propeptan on the uterus of an animal *parenterally* sensitized to egg white, or with egg white on the uterus of an animal *parenterally* sensitized to egg propeptan. W. Jadassohn and Schaaf<sup>5</sup> failed to take these principles into account when they disputed the type-specificity of propeptans, because these protein degradation products are unable to produce a positive Schultz-Dale test in animals sensitized to the native protein.

Our next problem was to determine how to prevent anaphylactic manifestations from making their appearance, following oral administration of a shock dose.

We could demonstrate that when orally allergized animals are given gradually increasing doses of food propeptans by intravenous injections at ten-minute intervals, the oral shock dose fails to elicit any clinical symptoms. When the animal is killed, two hours later, the Schultz-Dale test is found to be negative. The lung, however, is slightly but definitely inflated, a finding which indicates that the preparatory intravenous administration of propeptans has not satiated all of the antibodies.



*Experiment 4*

Guinea Pig No. 775 allergized to egg white orally. By mouth, every day for seven days: 1.0 c.c. of 25 per cent alcohol solution, followed immediately by 2.5 grams of egg white.

Three weeks later the following treatment was instituted.

Treatment: Intravenous injections of egg propeptan at ten-minute intervals.

Injection 1—Egg Digest representing 1.0 mgs. of Soluble Nitrogen—No reaction  
 Injection 2—Egg Digest representing 2.5 mgs. of Soluble Nitrogen—No reaction  
 Injection 3—Egg Digest representing 5.0 mgs. of Soluble Nitrogen—No reaction  
 Injection 4—Egg Digest representing 10.0 mgs. of Soluble Nitrogen—Slight bristling  
 Injection 5—Egg Digest representing 20.0 mgs. of Soluble Nitrogen—Bristling

After fifteen minutes—

Shock Dose: By mouth 7.5 grams of egg white.

Symptoms: No clinical symptoms.

Animal killed two hours after the oral shock dose.

Schultz-Dale Test: Negative.

Lung Perfusion Test: Slightly but definitely positive (Fig. 5).

Very similar results are obtained when the allergized animal is given only one oral dose of egg propeptan representing 20 mg. of soluble nitrogen + 0.2 grams of glycyrrhiza, dissolved in 3 c.c. of water, and then the shock dose by mouth after a sixty-six-hour interval. Here, too, the animal presents no clinical symptoms, but the lung is again moderately inflated.

*Experiment 5*

Guinea Pig No. 724, allergized to egg white orally. By mouth, every day for seven days: 1.0 c.c. of 25 per cent alcohol followed immediately by 2.5 grams of egg white.

Three weeks later the following treatment was instituted:

Treatment: By mouth, egg digest representing 20 mgs. of soluble nitrogen + 0.2 grams of glycyrrhiza + 3.0 c.c. of water.

*Sixty-six hours later*

Oral Shock Dose: By mouth, 7.5 grams of egg white.

Symptoms: Animal slightly restless, but otherwise no apparent change. Animal killed two hours after the oral shock dose.

Schultz-Dale Test: Negative.

Lung Perfusion Test: Slightly but definitely positive (Fig. 6).

Yet, when the oral shock dose is administered at some other time—for example, after an interval of twelve, twenty-four and forty-eight hours, there is pronounced inflation of the lung. The reasons for the necessity of waiting about sixty-six hours are not clear. However, our experience has shown that in guinea pigs this interval must elapse in order to protect the animal against the oral shock doses. This is, of course, quite different from the interval in human beings where three quarters of an hour was found to be the optimal time.

However, when the animals are given the propeptan orally on four consecutive days followed each time by the oral shock dose they will be entirely free from clinical symptoms on the second or third day. Lung perfusion tests performed on the fourth day will reveal no inflation of the lung whatsoever, a clear indication that the antibodies in the primary shock tissue (e.g. the lung) have been completely satiated.

*Experiment 6*

Guinea pig No. 749, allergized to egg white orally. By mouth, every day for seven days: 1 c.c. of 25 per cent alcohol solution, followed immediately by 2.5 grams of egg white. Three weeks later the following treatment was instituted:

Treatment: Daily schedule for four consecutive days.

5:00 P.M. Animal fed.

6:30 P.M. Food and bedding removed; animal kept in bare cage over night.

8:00 A.M. By mouth, egg propeptan representing 20 mgs. of soluble nitrogen + 0.2 grams of glycyrrhiza + 3.0 c.c. of water.

8:45 A.M. Shock dose, by mouth, 7.5 grams of egg white.

Symptoms: Slight restlessness and shaking of head after first administration of egg white. No clinical symptoms following the other oral doses of egg white.

Animal killed on the fourth day, two hours after the last feeding of egg white.

Schultz-Dale Test: Negative.

Lung Perfusion Test: Negative (Fig. 7).

However, the interval between the administration of the propeptan and of the oral shock dose must be no less than thirty minutes and no more than nine hours, otherwise the lung test will reveal marked inflation. In order to explain this rather puzzling finding we refer the reader to the theory of oral de-allergization.<sup>10</sup> This concept assumes that this form of de-allergization is accomplished by microshocks. The time of thirty minutes is probably necessary for the propeptan to neutralize (sate) the antibodies of the lung of the allergized animal while after nine hours this neutralization is broken up by the formation of newly formed antibodies in the primary shock organ. In addition, it is necessary to allow two hours to elapse between administration of the food antigen and performance of the uterus and lung tests.

When another food digest (e.g. chicken propeptan) was given instead of the egg propeptan, we observed pronounced clinical anaphylactic manifestations and maximal inflation of the lung in the lung perfusion test. Thus, the type-specificity of the propeptans was demonstrated once again.<sup>12</sup>

## SUMMARY

The conditions which lead to food allergy in human beings were reproduced in animal experiments. Animals were allergized *orally* by means of food proteins; allergic manifestations were elicited by *oral* administration of the very same food proteins, and these symptoms were inhibited by means of *orally* administered food digests (food propeptans).

By irritating the gastro-intestinal tract by means of alcohol, or by increasing the resorptive capacity of the intestinal mucosa by means of glycyrrhiza, it is possible to allergize guinea pigs orally to native food protein. After an interval of three weeks, food of the same type, administered orally, can evoke clinical anaphylactic manifestations and maximal emphysema in the lung perfusion test.

The observation was made that animals orally sensitized to food proteins to such an extent that they died instantaneously on intravenous injection of a very small amount of antigen invariably showed a negative

Schultz-Dale reaction, while the lung perfusion test was always positive. On the other hand, guinea pigs parenterally sensitized to a similar degree consistently exhibited both positive Schultz-Dale and lung perfusion test to the same oral shock doses. The mechanism underlying this difference is discussed.

In oral treatment food propeptans are effective only when followed after a certain interval of time by the corresponding food allergen *by mouth*. They will fully inhibit the clinical and characteristic pathological allergic manifestations, provided this procedure is continued for several consecutive days. Moreover, they will neutralize the antibodies in the primary shock organ, the lung, as evidenced by negative lung perfusion test.

The action of the propeptans is based on the principle of skeptophylaxis (anti-anaphylaxis) and leads first to temporary and later to lasting de-allergization.

It is highly probable that, in every-day life, oral de-allergization in human beings is brought about mainly by physiologically formed degradation products of food proteins digested in the gastro-intestinal tract, such as proteoses and peptones.

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# SENSITIVITY TO THE ORAL ADMINISTRATION OF CASTOR OIL

MAJOR PHILIP BLANK, MC

A SEARCH through the literature has failed to reveal any report of sensitivity to the oral administration of castor oil, although there is mention of many instances of contact sensitivity to castor oil and inhalant sensitivity to castor bean dust. A case of dermatitis medicamentosa due to the oral administration of castor oil was seen at the Station Hospital, Fort Eustis, Virginia.

## CASE HISTORY

A well-developed, white, male soldier, aged twenty-three, with no history of major or minor allergic episodes but with a history of fall type hay fever in a maternal uncle, received an ounce of castor oil in an outpatient infirmary. The patient had received no castor oil since childhood and could remember no untoward reaction at that time. Within twenty minutes after the administration of the drug, it was reported that the patient began having marked generalized abdominal cramps and diarrhea. Within two hours, the patient's tongue and fauces were reddened and slightly edematous. He developed a marked erythematous flush about the face. The patient was admitted to the hospital as a scarlet fever suspect about an hour later. On admission he presented a scarlatiniform rash over his face, neck and shoulders, moderate edema of both eyelids, lips and ears, a moderately severe stomatitis with reddening and slight edema of the fauces, and a slight generalized tenderness over his abdomen. The patient complained of a flushed, feverish feeling about his face and neck, especially of his ears and mouth, and of generalized abdominal cramps and some tenesmus. He was apprehensive and complained of marked generalized weakness. The admission temperature was 99.2 degrees F. by mouth and the pulse rate 100. Within three hours after admission, the patient developed a mild conjunctivitis, rhinorrhea of a clear watery fluid, a punctate vesicular papular rash over his neck and shoulders and a generalized extension of the erythema which resembled a scarlatiniform rash. Twenty-four hours after admission, the rhinorrhea and the conjunctivitis had subsided, the edema of the lips, ears and eyelids had regressed almost completely and the tiny vesicles were drying up. In forty-eight hours, a fine powdery desquamation began over his neck and shoulders and extended gradually over the entire body. The patient was apparently completely recovered in four days. The diagnosis of dermatitis medicamentosa was made and castor oil was suspected as the offending agent.

After allowing a three-day rest, the patient was given a clinical test with 4 c.c. of castor oil orally. The clinical picture seen previously was reduplicated exactly but to a slightly less degree. Desquamation again occurred. After three weeks, a third clinical test was given with 1 c.c. of castor oil. The patient developed erythema but without vesiculation, mild edema of the eyelids, mild cramping abdominal pains but no diarrhea and slight rhinorrhea. No desquamation developed.

The laboratory reported a leukocyte count of 5,800 cells and an eosinophilia of 6 per cent. Scratch-patch test showed only a slight reaction to castor oil. Patch test with castor oil was negative.

It is felt that the diagnosis of dermatitis medicamentosa due to the oral administration of castor oil was justified, and was sustained by repeating the clinical syndrome with two clinical trials of oral administration of castor oil.

This case is thought to be the first reported case of sensitivity to the oral administration of castor oil.

Major Blank is a Fellow of the American College of Allergists.

# Editorial

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## GRADUATE INSTRUCTIONAL COURSE

Pursuant to the College's policy of pioneering intensive graduate continuation courses in allergy in centrally located areas easily accessible from all parts of the country and Canada, its third course will be held at Thorne Hall, Northwestern University, Chicago, from Monday morning, November 5 to Saturday noon, November 10.†

Owing to its proximity to the Northwestern University Medical School, the Pearson Hotel, 190 East Pearson Street, is suggested for both students and instructors. In case the reservations there are filled, the applicants can be accommodated at either the Seneca Hotel, the Knickerbocker Hotel or the Drake. An informal dinner will be held Monday evening, November 5, at the Pearson Hotel so that the registrants may become better acquainted. The members of the Chicago Allergy Society have been invited to attend. Dr. William H. Welker, Head of the Department of Biological Chemistry, Director of Research of the Allergy Unit, and Dean of the University of Illinois College of Medicine, will speak at the dinner on "Antigenicity of Proteins in Relation to Allergy."

The most outstanding leaders in their respective fields are enthusiastic in their participation when making this one of the most outstanding graduate courses in allergy ever to be presented in this country. No effort is being spared to satisfy the registrants whether they are advanced students of allergy wishing to refresh their knowledge of the subject, those training for specialization in allergy, or the non-specialist seeking graduate training.

Seventy-two registrants attended the course conducted by the College in St. Louis last November. Of these members and non-members, twelve were in active service. Available outlines of the November courses (printed on sheets which fit a standard ring book) are still in demand. The Educational Committee urges that as many members of the College as possible, as well as candidates for Active and Associate Fellowships and non-members, avail themselves of this opportunity and register early, since registration of those outside the Chicago area may be limited by the Office of Defense Transportation. Hotel reservations should be made immediately.

All men in the Service at the time of their registration will be admitted without charge, otherwise the regular fee of one hundred dollars will be required. All registrants will receive outlines of the courses as well as the revised printed Manual of Allergy Laboratory and Diagnostic Procedures.

All those wishing to register for this course will please communicate with the Secretary, American College of Allergists, 401 La Salle Medical Building, Minneapolis, Minnesota.

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†See editorial in the May-June, 1945, issue of the ANNALS—Page 210.

## RESEARCH ON BLOOD GROUPS

Living tissue seems to have the general ability of reacting on the introduction of foreign matter with the production of proteins that can combine specifically with the matter introduced. It is well to keep aware of this fact because for a real understanding of immunological phenomena, it is essential to realize that antibody formation is a fundamental biological function without evident predetermined direction of action. Our mental makeup experiences the need of a purpose in all phenomena of life. In satisfying this need and also under the pressure of the practical needs of medicine, we have become used to split the biological phenomena connected with antibody formation into two compartments: One, we call immunology, and we tuck away in this compartment those antibody effects which seem to fulfill a useful purpose, particularly those cases where antibody neutralizes or contributes to destroy a microbial invader or its toxic products. The other, we call allergy, and into this compartment we sort out antibody activities which present a nuisance and sometimes a danger to life and happiness of man and his four-legged co-sufferers. The only *apparent* purpose of these phenomena in the established order of things is to provide for an interesting specialty in the profession of medicine.

There are antibody-antigen reactions that do not fit in either compartment. Some of them we produce experimentally and they are particularly favorable objects for the study of basic problems of antibody action. Others are offered to us by nature and a closer acquaintance with these is very much worth while just because they shake our belief in the purposefulness of this peculiar system of physiological activity. Among these, the study of blood-specificity is of particular interest (*and* of great practical importance).

Our readers will have found in the preceding issue of this journal, a review by A. S. Wiener concerning one of the most recent developments in this field, namely, the Rh factors. The author of our article has presented a synopsis of the whole field of research on blood-specificity in a book\* which makes very good reading indeed, and which we would wish to see in the hands of many of our colleagues. This book unfolds the story of over 40 years of patient unraveling of one puzzling phenomena after the other. The discoveries of the various types of blood-specificity—the basic A-B-O system, the factors M, N and P, and the youngest member of the family, the Rh factors—have deeply influenced our thinking about the problems connected with individuality and heredity. The field of blood group research has presented particularly favorable conditions for the application of exact statistical and genetic analysis, and these methods have been employed with remarkable suc-

\*Wiener, A. S.: *Blood Groups and Transfusions*. Third edition, XIX, 438 pages, 69 figures, 106 tables. Springfield, Ill.: C. C. Thomas, 1943.

cess. Clinical allergy could greatly profit by adopting similar points of view and methods of research.

The case of blood-group research demonstrates what can be done when the right man gets a real chance to go to the roots of a great problem. The result was a golden harvest of theoretical and practical results. Clinical allergy has accumulated an enormous and sometimes confusing mount of observational material. What is needed is the strengthening of the foundation on which our house is built. This is only possible by fundamental research carried on without regard to immediate application. The future development of our field makes it imperative to invest in sustained curiosity, that is, to foster working conditions conducive to long-range and consistent investigational effort. The policy of the College in this respect is very definite. It has found its first expression in collecting means for research fellowships, and in efforts to bring the clinical allergist in contact with related fields and with science in general.

A. J. WEIL

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### THE MANUAL OF ALLERGY LABORATORY AND DIAGNOSTIC PROCEDURES\*

This practical, new, revised Manual, compiled by members of the College, is ready for mailing. The supply of the first mimeographed edition, issued at the St. Louis instructional course last fall, having soon become exhausted, a second enlarged, printed, loose-leaf edition (8½ x 11), permitting supplemental or revised procedures, has been published. It is bound in a standard ring book of exceptional, durable quality. The Manual includes detailed methods of making allergenic extracts of all kinds and their standardization. The table of contents is a complete guide to the material included.

Laboratory procedures for preparing allergenic extracts and their application, various methods of testing and the treatment of allergies, the technique of pollen surveys and miscellaneous information valuable to students of allergy are briefly described therein. This condensed information is based upon knowledge gleaned from authoritative textbooks and other published articles on the subject as well as years of personal experience of the collaborators, with the hope that it will save valuable time. For detailed description, however, the reader is referred to the many excellent texts on the subject.

Published in loose-leaf form, it readily enables supplementary information from time to time, as occasion arises, in order to present a concise, up-to-date Manual.

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\*See page 331 of this issue for a review of the Manual.

# Progress in Allergy

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## ALLERGIC SKIN DISEASES

### Eczema—Urticaria—Drug Eruptions A Critical Review of Recent Literature

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#### ECZEMA—ALLERGIC DERMATITIS

A definition of terms was presented in last year's review.<sup>38</sup> It must suffice to repeat that eczema and allergic dermatitis are used practically as synonyms. The term eczema is used morphologically to denote a superficial inflammation of the skin with or without vesiculation, more or less sharply outlined, acute, subacute or chronic, usually itching at one time or other, and in many instances recurring. Eczema will be reviewed under the following four headings: (1) Atopic Dermatitis, (2) Contact Dermatitis (Epidermitis), (3) Microbic (mycotic, bacterial, parasitic) Eczema, and (4) Other Forms of Eczema.

#### • ATOPIC DERMATITIS

The distinction between atopic dermatitis (neurodermitis) and contact type dermatitis (epidermitis) is challenged by Cooke.<sup>19</sup> He claims that these two forms of eczema are immunologically identical and suggests that the terms atopic dermatitis and neurodermatitis should be eliminated. Cooke maintains that atopic dermatitis (also in older children and adults) has no known points in common with hay fever and other wheal-producing allergies. This claim is partially based on the fact that the result of the scratch or intradermal test is a wheal and not an eczema. "With the tests we should seek to duplicate (reproduce) the essential characteristics of the clinical reaction." (Cooke's requirement, if taken literally, would also challenge the value of a scratch test as a diagnostic aid in hay fever or asthma.) Cooke has never observed an exacerbation of eczema from the ingestion of the foodstuff which gave an immediate wheal reaction. He too stresses the frequent association of eczema and wheal-reacting allergies in the same infant, but cannot explain it with his theory.

Those who distinguish the atopic form from etiologically different forms of the so-called infantile eczema, are aware that a positive intradermal or scratch test usually (in infants as well as adults with atopic dermatitis) produces a whealing reaction and only rarely a delayed eczema-like reaction. On the other side, most of these patients do *not* present clinical signs of urticaria. These facts by themselves are no proof or even an indication that the two phenomena (whealing test and atopic eczema) are not related. I may mention an analogy in sunlight allergy.<sup>37</sup> There are cases of light dermatitis (prurigo estivalis as well as hydroa vaccini-formis) that clinically present only symptoms of an eczema or a papular or vesicular eruption and no wheals. The skin tests with ultraviolet light performed on normal skin in many of these cases produce only an immediate whealing reaction. Urticarial ultraviolet reactions are so rare that there cannot be any doubt as to their etiological relation with the eczema- or prurigo-like type of eruption from which these patients suffer.

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\*From the Marshfield Clinic.



The reader will find some of the facts and reasons that urge a separation of atopic dermatitis and contact type dermatitis in last year's review<sup>38</sup>; the question of their interrelation also has been discussed. The difference of the two forms may not be as fundamental as generally thought. The possibility of epidermal sensitization in atopic dermatitis must be admitted. MacCardle, Engman and Engman<sup>83</sup> believe that the development of a lesion in neurodermatitis (atopic dermatitis) is located in the spinous cells of the epithelium. On the other hand, the occurrence of dermal sensitivity in contact type dermatitis is a fact, shown especially in epidermitis due to sensitivity to nickel or chromates. One may agree with Cooke<sup>19</sup> that the paucity of our knowledge has led to confusion. Some of the present concepts need revision. Cooke's arguments will stimulate discussion. But at this juncture it does not seem justified to throw overboard the distinction between atopic skin sensitivity and contact type sensitivity and their manifestations—a distinction which constitutes perhaps the greatest practical advance of modern dermatology.

A histologic attempt at differentiating various forms of eczematoid dermatoses is presented by Sachs, Miller and Gray.<sup>112</sup> Contact dermatitis (epidermitis) is characterized by small vesicles, frequently in the upper part of the epidermis, little or no acanthosis (thickening of the epithelium), and a mild superficial inflammatory reaction. In contradistinction, atopic dermatitis has a nonedematous regular acanthosis, thickening of the walls of the small arteries and a focal cellular reaction. The pathological features of nummular eczema appear to be chiefly those of neurodermatitis (atopic dermatitis) plus an epidermic vesicle. In addition to these three forms of eczema the authors describe a fourth one which they call eczema (without any further specification). It differs from the other three by an extensive cutis reaction, with special involvement of the capillaries. This study confirms the principal histologic differences between clear-cut cases of contact dermatitis and atopic dermatitis. However, morphological histopathology offers little help for investigation of the numerous atypical or combination of forms of eczema.

Histochemical studies may be more promising. It has been shown by MacCardle, Engman and Engman<sup>83</sup> that magnesium deficiency is found in active atopic skin lesions. Sullivan and Evans<sup>129</sup> compared atopic dermatitis with experimental magnesium deficiency in rats. The authors conclude that it was not possible to establish the claim that these two conditions are identical or similar diseases. The clinical symptoms and the microscopic changes are dissimilar in the two conditions. Furthermore, in the experimental disease of the rat there is a decrease or absence of magnesium in the blood but not in the skin, whereas in atopic dermatitis of humans there is a decrease or absence of magnesium in the skin but no change in the blood level.

*Atopic Dermatitis by Contact.*—It is important to distinguish between "atopic dermatitis by contact" and the so-called "contact dermatitis." The essential shock organ in atopic dermatitis is the vascular-connective tissue layer, in contact dermatitis (epidermitis) the epidermis (epithelium). The route of the allergen is immaterial. Contact type dermatitis may be caused by internal application<sup>19</sup>; on the other hand atopic dermatitis may be produced by external contact. The most common examples perhaps are milker's eczema (with positive scratch or intradermal tests to cattle dander) and the atopic form of plant dermatitis. Mitchell and Mitchell<sup>89</sup> report a case of recurrent seasonal dermatitis in which the protein fraction of timothy pollen was the offending cause. This is an instance of atopic dermatitis by contact. These cases are apparently more frequent than recognized. It is important to draw attention to this atopic form of plant dermatitis because the majority of eczemas from grasses and weeds are different and due to contact type sensitivity to the oleoresins of the plants. Herrmann, Sulzberger and Baer<sup>60</sup> report several cases of atopic dermatitis by contact. These authors report penetration of allergens into the human skin by means of new penetrating vehicles. Skin

tests performed with these vehicles produced urticarial reactions of considerable extent appearing within two to five minutes after inunction. The results corresponded closely to those obtained in the same cases with scratch tests. Percutaneous penetration has again been studied by McKee, Sulzberger, Herrmann and Baer.<sup>84</sup> By using vehicles which utilized the combined and reciprocal action of water, propylene glycol, interface active agents, coupling agents and solubizers, staining of the follicles, cutis and epidermis was regular. However, in all instances a color-free band beneath the horny layer and above the prickle cell layer (approximately corresponding to the stratum lucidum) was observed. The authors conclude that this band is a barrier for percutaneous penetration. These results indicate that penetration occurs through the hair follicles into the cutis; there seemed to be an upward movement of the colored material from the cutis into the epidermis.

*Infantile Eczema.*—Infantile eczema is by no means always a manifestation of atopy. It can rather readily be divided clinically in four groups<sup>35</sup>: (1) Atopic dermatitis, (2) Seborrheic dermatitis, (3) Contact dermatitis (epidermitis), (4) Infectious eczema (chiefly that form called intertrigo).

Plotz<sup>106</sup> reports two cases of eczema of face, neck and arms in infants under one year which were caused by contact with the mother's hair. The hair lacquer used by the mothers was found to be the cause. Jerome Glaser<sup>50</sup> obtained splendid results in two cases of severe infantile eczema with a synthetic milk containing meat particles. These infants had not been relieved by soybean milk. Unfortunately the manufacture of this milk substitute has been discontinued on account of the war. Strickler, Herman and Grumach-Fabian<sup>127</sup>, studying forty-one children from nine months to twelve years with eczema (35 atopic, 4 seborrheic, 2 ichthyotic), and nine controls failed to find any deviation of the gastric secretory function in this series.

Many physicians are reluctant to hospitalize patients with infantile eczema. M. A. Green<sup>55</sup> reports a case of a seven-months-old girl whom he had to hospitalize on account of generalized atopic dermatitis. The child developed measles and bronchopneumonia, but eventually recovered. Epstein<sup>35</sup> has investigated hospital mortality and morbidity of infantile eczema. He reports a series of 100 consecutive hospital admissions without a death from 1937 to 1944. Out of these children, twenty-one suffered from twenty-three complications, a morbidity of 23 per cent. A breakdown of the statistics showed that all but one of the complications occurred among the seventy-eight atopic children and only one among the twenty-two nonatopic eczemas. Nearly all complications were respiratory infections or gastro-intestinal disturbances. They are explained as exacerbations of concomitant respiratory or gastro-intestinal allergy. The author concludes that with the advent of sulfonamides and under proper nursing care, there need not be fear of death in hospitalized infants with eczema. This conclusion should not lead to indiscriminate hospitalization of cases of infantile eczema, but it should eliminate fear in those instances where hospitalization becomes mandatory on account of the severity of the eczema, or for other reasons. The so-called "sudden death from eczema" in infants is also discussed.<sup>35</sup> A hypothesis of toxic effects from phenol-like tar products, in combination with interference with skin respiration and disturbance of the autonomous nervous system, is suggested to explain some instances of this phenomenon. A reminder is given about the toxicity of coal tar and it is suggested that tar preparations should not be used over too great surfaces. Strickler<sup>125</sup> reports five cases of Kaposi's varicelliform eruption. Four of Strickler's cases occurred in infants and children suffering from eczema. They all recovered. His first case, however, followed smallpox vaccination and ended fatally. As we know now that true Kaposi's varicelliform eruption is caused by the virus of herpes simplex, this case belongs to eczema vaccinatum.

*Psychosomatic Aspects of Allergic Dermatoses.*—The role of psychological factors in dermatoses has long been recognized by some authors. But only in recent years has this aspect received general recognition, under the title of psychosomatic medicine. Evidence for neuropsychiatric disturbances in skin diseases has been presented in the form of studies of groups afflicted with allergic eczemas, by case reports, and by experiments studying the physiological effects of emotions.

Lynch, Hinckley and Cowan<sup>80</sup> present psychobiologic studies of seventeen patients with atopic dermatitis. Thirteen suffered from typical atopic eczema (disseminated neurodermatitis), four presented less extensive eczematous eruptions that were classified as late exudative diathesis of Rost. A definite psychosomatic relationship seemed apparent. The findings would support a concept of dynamic relationship in which constitution, specific allergic sensitizations, personality, and environmental stresses play roles of varying degree in each individual's total reaction and eczema. Physical similarities and tendencies were present in atopy, vigor, rapid pulse rates, good exercise response, lowered basal metabolic rates, and low white blood cell count and all the patients demonstrated suppressed resentment and tension, and all but two had more than average intelligence. Certain other personality factors were commonly present but appeared to be less constant and of less importance. These included appreciable but varying degrees of purposefulness with limited spontaneity; superficial emotional stability and high reactivity; and tendencies to perfectionism, self exaction, and self assertiveness.

Greenhill and Finesinger<sup>57</sup> found that patients with atopic dermatitis show psychoneurotic symptoms more frequently than do the controls. The patients with atopic dermatitis were found to have hostile tendencies, feeling of inadequacy and depressive trends. In these patients was a definite correlation between events which evoked feelings of anger and depression, and exacerbations of the skin eruption. According to Kendall<sup>71</sup> suppressed resentment is the outstanding emotional feature.

A direct effect of psychologic factors is indicated by the following case reports. Wright<sup>143</sup> reports two cases of a psychic etiology in acute dermatitis. Here is the history of one: A man, aged sixty-seven, developed an acute vesicular eruption on the hands and feet within twenty-four hours after his oldest daughter was involved in a serious automobile accident. There was no history of any kind of previous skin eruptions. The daughter recovered and after three weeks of local therapy the eruption disappeared. A year later a younger daughter was seriously injured in an automobile accident and within a few days the eruption reappeared in full bloom. After recovery of the daughter the eruption disappeared and there has been no recurrence since. Epstein<sup>42</sup> reports a case of an eczema of the hands that apparently was caused and maintained by a variety of factors. One evening the patient had a heated argument with a neighbor family about the strained relations of their respective daughters, at the end of which he threw his neighbor out of the house. Within an hour he noticed a papular rash appearing all over his body and shortly afterwards a severe flareup of the eczema of his hands which had nearly disappeared by that time. The role of psychic factors probably is most pronounced and most important in that condition commonly called neurotic excoriations. Although there is no evidence of allergic skin manifestations in most of these cases, they are sometimes mistaken for eczemas and probably concern the allergist as well as the dermatologist. A. Carley<sup>15</sup> presents a psychiatrist's analysis of such a case. The patient was a married woman, forty-nine years of age, who suffered from severe pruritus for four years, and was treated by many physicians apparently without success. Carley analyzes her as a woman, who because of her early rejection by her parents (she was an unwanted sixth child), learned to react to her environment in an aggressive manner. Her parents were emotionally immature and from them she learned

similar inadequate methods of handling her problems. As long as her aggressiveness met with success she remained fairly well adjusted. But when her aggressiveness failed to gain satisfaction (as in bossing her son) she reacted in a more inadequate manner as expressed in her symptoms of severe itching necessitating the personal discomfort of resulting skin lesions along with the undesirable feelings of depression. With the understanding of the situation the patient's symptoms disappeared, but more important, she, her husband and son have spent the most happy six months of their family life.

Mitchell and Curran<sup>88</sup> present an outline of a method of psychotherapy suitable for the allergist. The patient is encouraged to express his feelings freely. Besides the patient is aided to see the fundamental drives and desires behind his emotions. The patient is assured that his talking so freely has been worth while and that he has not been acting foolishly. However, the patient usually does not accept the psychogenic factors and has his own physical diagnosis of himself. Gradually, however, he becomes encouraged and he begins to talk about his home, family, work, personality needs. Slowly he accepts some of these factors as part of his problem. Some of these patients require the help of a psychiatrist; as a rule—as Kendall<sup>71</sup> states—the search for the focus of suppressed emotion with insight into the frustration circumstance, all are within the ability of the dermatologist or other specialist if he will but take time to listen to the patient.

There are some experimental studies that help to understand the mechanism of psychosomatic relations. Eugene E. Bereston<sup>8</sup> presents an interesting contribution to the influence of the nervous system on skin reactivity. Bereston compared various skin reactions, namely, the histamine flare, the pilomotor reaction to acetylcholin, as well as tuberculin, trichophytin and contact type reactions on patients with hemiplegia and paraplegia. The histamine and cholin reaction was diminished in a high percentage of cases in which nerve degeneration has occurred, that is, in paraplegic individuals. In patients with hemiplegic lesions (located in the brain) in which the peripheral nerves are not degenerated, no such changes were noted. Intradermal reactions to tuberculin and trichophytin showed the same behavior; here too the reaction depends on the degree of integrity of the peripheral nerve axons and the adequacy of the peripheral circulation in paraplegic cases. In experimentally produced contact dermatitis the results were somewhat different; in paraplegic individuals with transverse cord lesions, ten out of the twelve sensitized patients showed stronger reactions on the normal skin; but changes were also noted in hemiplegic patients. In all sensitized cases the skin of the normal knuckle gave a greater reaction to the test dose than did the skin of the affected side. In sharp contrast to these reactions, in experiments with ultraviolet the sunburn-reaction tended to be stronger on the affected skin sides in both hemiplegics and paraplegics. This difference from the histamine reaction appears especially interesting in view of the claim that histamine is responsible for the sunburn reaction.<sup>33</sup> The influence of local anesthesia on experimental contact dermatitis has been studied by Mom and Noussitou.<sup>94</sup> This author found diminished reaction at the site of local anesthesia. Mom and Noussitou<sup>94</sup> performed experiments regarding the influence of the peripheral nervous system on urticarial reactions of the skin. They conclude that the experimental urticarial reaction of the skin is partially controlled by the peripheral nervous system. Blockage of the peripheral nerves by local anesthesia delays and limits appearance and spread of erythema and swelling following intradermal injections of histamine and morphine.

A psychosomatic effect of emotional stress upon the temperature of the skin has been demonstrated by Mittelman and Wolff<sup>90</sup> during psychotherapeutic (psychoanalytic) interviews. The temperature as recorded in the fingers fell in emotional stress with predominant anxiety, embarrassment, humiliation, anger, de-

pression with hostility, guilt and fear of abandonment. In states of emotional detachment—in spite of situations of stress—the finger temperature was high and relatively even. During sexual excitement, there was a rise above the control level. Such an observation of local vascular changes would present some physiological background for the often observed effect of emotions on eczema of the hands. Mom and Noussitou<sup>93</sup> were able to produce positive patch test reactions in persons sensitized to dinitrochlorobenzene by application of saline solution by suggesting that they had applied the chemical. These interesting reports so far have not been confirmed by others. Zeller tried unsuccessfully to repeat Clarkson's<sup>16</sup> experiment who had reported disappearance of a positive intradermal reaction to egg in deep hypnosis. In five experiments, hypnotic suggestion failed to affect the usual response of passively sensitized skin areas, and also failed to affect the skin of patients sensitive to ragweed or to animal dander.

*Skin Tests.*—There is still quite a controversy about the value of dermal tests (scratch tests and intracutaneous tests) in eczema, especially atopic dermatitis. Sulzberger and Baer<sup>134</sup> present a review of these methods from the standpoint of the dermatologist, with many helpful practical suggestions; their evaluation of these tests appears rather conservative. The reviewer admits readily that the scratch and intradermal tests are far behind the patch test in dermatologic value, but he is convinced that they are of more help in typical as well as atypical manifestations of atopic skin sensitivity than is generally realized by the dermatologist, and of less value than is assumed by many allergists.

*Treatment.*—Coal tar is still the best topical medication in atopic dermatitis, especially in children. A brief study of its manufacture, composition and use in industrial dermatitis is presented by Frank C. Combes.<sup>18</sup> In view of the fact that coal tars from different sources may vary in their carbon content from 5 to 35 per cent, he recommends Daxalan, a commercially manufactured coal tar paste that contains 3 per cent coal tar (low in naphthalene content) 5 per cent zinc oxide and 50 per cent starch in a special hydrophylic base. One should not forget that coal tar is a rather toxic substance, and should not be used on too large surfaces, especially in infants.<sup>35</sup>

Hapamine, the antigenic histamine compound, has aroused great hopes for the treatment of atopic dermatitis. There is quite an argument regarding the efficacy of this drug and the dangers accompanying its use. Rowe's<sup>110</sup> therapeutic trials with hapamine in over 25 patients were uniformly unsuccessful, except for evidence of slight possible benefit in a few cases of atopic dermatitis. His series consisted of various allergic diseases which had not responded to the regular allergic methods. Some authors have reported severe reactions. Braden<sup>12</sup> observed a most severe constitutional reaction following an intradermal test with 0.02 c.c. hapamine. He believes the risk is too great to justify the use of this drug. Rowe<sup>110</sup> states that hapamine is being unwisely recommended, and that the medical profession will again be disappointed and disillusioned as in the case of torantil. Epstein<sup>41</sup> observed in a patient suffering from urticaria very severe whealing reactions from hapamine even in dilutions up to 1:1000. This patient was not abnormally sensitive to histamine and did not react to the refined horse serum, used in the manufacture of hapamine.

There is no doubt that hapamine does not live up to expectations. On the other hand it does not appear to be without merits. There seems to be a general impression that it is of some value in atopic dermatitis and in chronic cases of contact dermatitis. The reviewer has also seen some rather favorable results in a few instances.

Severe untoward reactions can be avoided by not treating hapamine sensitive persons. If a scratch test with horse serum, and a subsequent intradermal test

with diluted hapamine is negative, one should be on safe ground. The need for greater individualization of dosage is now recognized in the manufacturer's directions.

## CONTACT DERMATITIS (EPIDERMITIS)

(Eczematous Contact-type Dermatitis, Dermatitis Venenata,  
"Ekzem" of the European School)

The term "epidermatitis" to designate manifestations of epidermal sensitivity is suggested by Templeton<sup>137</sup> in order to separate it from skin disorders caused by dermal sensitization. This proposal emphasizes the need to replace the ambiguous term of "contact dermatitis"<sup>38</sup>, because it conveys the wrong impression that external contact is its characteristic. However, the route of the allergen is immaterial<sup>10</sup>, it is the shock organ and other immunologic factors that separate "contact dermatitis" from atopic dermatitis.<sup>38</sup> Epidermitis (contact dermatitis) is mostly but not always based on allergy. Primary irritating substances may produce an identical morphological picture. Neither is there a histopathological difference between the allergic and toxic forms of contact dermatitis. Mom and his co-workers<sup>92</sup> studied the histopathologic changes produced by primary irritation from dinitrochlorbenzene diluted 1:20 and those by an allergic reaction of a weaker dilution. The lesions produced by the primary irritation are identical with those obtained after sensitization by dinitrochlorbenzene through an allergic mechanism. The picture always consisted of the formation of spongiosis and intraepidermal vesicles invaded by polynuclears and lymphocytes. It was followed by lymphocytic perivascular infiltration of the dermis.

Last year's literature on epidermitis (contact-type dermatitis) consists largely of reports about allergens encountered in military and private life, and industry.

*Clothing.*—Dolce<sup>28</sup> reports ten cases of shoe leather dermatitis with the typical location on the sides and dorsa of the feet, toes, and ankles. All these patients had an associated hyperhidrosis. Treatment of the hyperhidrosis and a change of the type of shoes proved effective. A case of dermatitis from stocking dye is reported by Hollander.<sup>61</sup> The diagnosis was confirmed by a positive patch test. The sensitization to Tintex dye followed an accidental cut. The role of accidental injury in producing sensitization to chemicals that have been tolerated for a long time previously, should be remembered by all those who take care of cases of industrial dermatitis. Many cases of contact dermatitis from clothing are seen in the army and navy. Carpenter and Banzer<sup>14</sup> report three cases of contact dermatitis from blue uniforms in Navy personnel. Patch tests with their own uniform clothes gave a severe reaction. Dermatitis, wholly or partly due to intolerance by the skin of contact with woolen textiles apparently plays a great role in the British army according to Davies and Barker.<sup>23</sup> During eighteen months they collected 201 cases. They made up a high proportion (16.4 per cent) of the skin patients in one large military hospital, 110 out of 670 admissions. The eruption presents itself in various forms, some cases simply as pruritus or as an urticarial eruption; most cases as various forms of dermatitis. An important manifestation was that of prurigo simulating scabies. The diagnosis was established in most instances either by positive patch tests or by exposure to the khaki material. The prurigo-scabies-like cases gave only faintly positive patch tests and have a tendency to recover with lapse of time. The authors believe this dermatitis chiefly due to intolerance to wool; sensitization may occur spontaneously or as the result of friction by garments, but more commonly its onset is determined by some other dermatosis, mainly, scabies. As the description of Davies and Barker's cases indicates, they belong to different forms of sensitivity, among them, contact, atopic, and mechanical. These authors recommend removal of the irritant

and protection with cotton underwear. Vitamin B and C had no effect in their experience. M. T. Lowance<sup>79</sup> reports three cases of severe dermatitis of the face and neck in children wearing Halloween masks.

*Cosmetics.*—Howell<sup>64</sup> reports a case of dermatitis of face, neck and ears following "cold permanent waving." Skin test demonstrated that the patient was sensitive to a preliminary lotion, but not to the actual cold waving compound. Howell does not mention of what the preliminary lotion consisted. Keil and Van Dyck<sup>70</sup> found that twenty-five of twenty-six nail polish sensitive patients reacted to patch tests with toluene sulfonamide resin. None of the patients were found sensitive to nail polish remover.

Various chemicals: Forman<sup>44</sup> stresses the fact that contact dermatitis may first or chiefly appear not on the hands that touch the agent, but on those parts of the body that are touched by the hands. He reports a case of acute dermatitis of the left orbit, lobe of left ear and adjoining cheek in a man who was sensitive to self-striking matches. He kept the box in the left-hand trouser pocket and had the habit of holding his face in his left hand while sitting. "Diaper rash" usually means a dermatitis of the diaper region in babies caused by the irritation of decomposing urine. Dobes<sup>27</sup> describes under this title five cases of an acute dermatitis in infants from two to sixteen months of age. The diapers had been passed through an antiseptic rinse. The antiseptic, "Perm-Aseptic" is a primary skin irritant in strong concentrations and a sensitizer in weak solutions. The etiologic relationship was proved by a positive patch test in one of the cases.

Investigation of the causes of contact dermatitis of the hands is often a very difficult problem. Sterling<sup>128</sup> found sensitivity to "Microlene," a germicidal powder used in dishwashing, as cause of a severe, long-standing dermatitis of the hands, arms and neck of a waitress. According to Anderson<sup>2a</sup>, the true nature of the contact dermatitis of the feet and hands due to rubber is frequently unrecognized. Rubber cement and elastic rubber fabrics are used in the manufacture of shoes, especially of women. The commonest sites involved are the toes and the sides of the heels.

*Drugs\*.*—Pyle and Rattner<sup>109</sup> report the first case of epidermitis (contact dermatitis) from penicillin. The diagnosis was corroborated by a positive patch test with crystalline penicillin. Binkley and Brockmole<sup>9</sup> report two cases of dermatitis from penicillin in physicians who handled solutions of sodium penicillin. In one case both patch tests and intradermal tests were strongly positive. Face, eyelids and penis apparently are the favorite location of dermatitis in workers handling penicillin. Silvers<sup>123</sup> reports another case. As a patch test with commercial penicillin was positive, whereas a solution of pure crystalline sodium penicillin did not produce a reaction, it was concluded that the dermatitis in this instance was caused by an impurity.

Orland, Flesch and Rothman<sup>99</sup> tested a dentist who developed dermatitis from contact with procaine hydrochloride. He gave also positive tests to butyn, tuto-caine, pontocaine, monocaine, larocaine. Many compounds related to procaine were tested; only those reacted that contained an aromatic amino group on the benzene ring and only when the amino group was in the para position. Dore, Prosser and Green<sup>29</sup> report nine cases of morphine dermatitis in a morphine factory. The eruption normally started about the eyelids; the neck was also a common site. The arms and hands were usually affected last. Hollander<sup>62</sup> describes a case of persistent dermatitis of the flexor surfaces of the fingers. It was caused by application of tincture of merthiolate over a period of two years. The eruption was confined

\*Eruptions caused by the medical use of drugs are reviewed in the chapter "Drug Eruptions." (See page 317.)

to the distal phalanges. A patch test with tincture of merthiolate was positive. Avoidance of the medication was followed by rapid improvement.

*Plants.*—Epidermitis (contact dermatitis) from lemon grass oil in eight workers is reported by Mendelsohn.<sup>86</sup> The men had worked on a boat from India which had tanks with lemon grass oil on board. The dermatitis was similar in appearance to poison ivy dermatitis. Since lemon grass oil has many uses, it should be remembered when searching for etiologic agents in contact dermatitis. Lockey<sup>77</sup> reports an outbreak of contact dermatitis, which occurred among men handling varnish containing cashew nut oil, and which was found to be due to faulty treatment of the oil in the manufacturing process. Positive patch tests were obtained with this varnish and with cashew nut oil, but not with properly prepared varnish. Intramuscular injections with cashew nut oil extract accelerated the "hardening" and "desensitization" of sensitive individuals who worked with cashew nut oil. Merrill<sup>87</sup> describes dermatitis caused by various representatives of the Anacardiaceae in tropical countries. These plants cause a distinct and often severe dermatitis corresponding to Rhus dermatitis in the United States. The various species belong in the same family, the Anacardiaceae, and the active principle is the same in all cases. The resinous sap of these plants possesses the dermatitis-producing properties. Various species of the mango tree, producing the familiar mango dermatitis, also belong to this family. The question whether smoke from poison ivy is capable of producing a dermatitis has been investigated again by Howell.<sup>65</sup> His results are interesting both from a theoretical and practical viewpoint. Smoke filtered through cotton did not produce a dermatitis in seven sensitive volunteers. Three additional students acquired a mild dermatitis on the forearms held directly over the flame of the burning ivy. Apparently small particles of leaves, soot and charred matter carried by the smoke were responsible. These experiments indicate that while the actual gaseous smoke or the fumes from burning poison ivy are harmless, people who are burning poison ivy might get a dermatitis from that mixture of gases and particles that is called smoke in common language.

*Industrial Dermatitis.*—A program for prevention of irritation and sensitization of the skin to chemical compounds is presented by Leon Goldman.<sup>51</sup> There is a great variation in the incidence of occupational dermatitis in plants with different hazards. Schwartz<sup>117</sup> states that there is comparatively little dermatitis occurring in the manufacture of synthetic rubber despite the many irritant chemicals used. Most of the occupational dermatitis occurring in the manufacture of buna S is caused by chemicals added to butadiene and styrene in order to make the reaction possible. Schwartz describes the process of manufacturing and processing synthetic rubber and the numerous chemicals involved. He explains the low incidence of dermatitis in factories making synthetic rubber by the fact that these plants are modernly equipped with mechanical safety devices, and that the safety recommendations are carried out in these factories.

Contact dermatitis from synthetic resins and their manufacture is playing an increasing role as these plastics find a wider field of usefulness. Lockey<sup>78</sup> describes the composition, uses, and the manufacturing processes of the principle synthetic resins (plastics) and presents suggestions for the prevention of dermatitis in workers handling these resins. Anyone who has experience with this type of dermatitis will subscribe to the following recommendations: Persons with an allergic background or suffering from skin diseases should not be employed in the plastic department. Protective clothing with long sleeves should be provided. Facilities should be furnished so that the worker can change from his street clothes to his working clothes. The lockers for street clothes and work clothes should be in separate rooms with a shower bath between them. The dust and fumes in



the work rooms should be removed by intake exhaust fans. Abrasions or skin breaks in workers should be treated immediately as sensitization often starts at the site of such an injury.

Sulzberger<sup>132</sup> mentions the following plastic articles which he has found as cause of epidermitis in recent years: (1) clothing finishes (shorts, stockings, shirts, pajamas, et cetera.), (2) nail lacquers, (3) hair lacquers (pads), (4) lacquers on feathers, hats, et cetera, (5) lacquers on hair pins, (6) wrist watch straps, garter straps, and belts, (7) bottle caps, (8) buttons, (9) artificial jewelry of various kinds, spectacle frames, et cetera, (10) steering wheels, (11) ear-pieces (of hearing devices, radio receivers, et cetera), (12) false dentures (plates), (13) instruments (physicians', dentists', et cetera), (14) toys and lacquered objects used in games, (15) toilet seat and other paint and furniture lacquers.

Sudden outbreaks of dermatitis in industrial plants frequently present a puzzling problem. Sometimes all one finds is a variety of unrelated dermatoses, and actually there was no special increase, but someone in the plant got conscious of the number of skin cases. However, in many instances, the introduction of new processes or the changes in the composition of chemicals may produce a sudden outbreak. Schwartz<sup>118</sup> reports such an occurrence in a plant manufacturing hydrochloric acid. The change in the process consisted of the addition of soft coal. Schwartz found that a waxy deposit was the cause of the dermatitis. It contained 5 per cent hydrochloric acid. Schwartz and co-workers<sup>120</sup> report allergic contact dermatitis (allergic epidermitis) occurring in a plant that manufactures cemented carbides. Sensitivity to cobalt was found to be the cause of the dermatitis. In a number of cases the eruption was limited to the anti-cubital spaces; in others to the sides of the neck and the eyelids; while in still others the flexor portion of the forearms and backs of the hands were affected. In a few cases the eruption was generalized. The authors recommend thorough elimination of dust and protection from dust for the workers. Some of the workers developed a tolerance. Natural desensitization in workers apparently occurs much more frequently than is generally recognized. Peck, Gant and Schwartz<sup>100</sup> present a report on the subject of "hardening" in industrial allergic dermatitis. Jadassohn in 1923 used the term hardening (Abhärtung) to describe the development of tolerance to sensitizing chemicals in industry. Peck, Gant and Schwartz have observed instances of "hardening" practically in all industries where there are allergic dermatoses. The authors cite a few of these observations in the manufacture of synthetic resins, tetryl, and TNT. Up to 85 per cent of the workers who suffered from allergic dermatitis were able to return to the old contacts without any ill effects. Keil<sup>69</sup> however expressed skepticism that "hardening" actually occurs. The report by Peck and co-workers should stimulate further trials of desensitization in industrial as well as non-occupational contact dermatitis.

*Patch tests.*—Gaul<sup>49</sup> adds a "past-treatment patch test" to the list of patch test uses. This is a recommendation to test previously used medications in order to find those to which the patient may be allergic and to avoid their further use. There is some argument among dermatologists as to the advisability of such a procedure, partially based on potential dangers of such testing. The reviewer agrees with Gaul's recommendation. By performing patch tests at the appropriate time, and by using only small quantities or weak dilutions in cases of a suspected strong sensitizer, the danger of severe flare-ups or serious side effects can be almost completely eliminated. On the other hand, such testing has been very helpful to the patient in cases where medications other than those suspected were found to be the sensitizer. Last, but not least, the production of a localized dermatitis by the patch test will make the patient more prone to avoid future contact with this medication, than a warning based only on a more or less founded suspicion. Sulz-

berger and Baer<sup>134</sup> present a critical review of the uses of the patch test, such as differential diagnosis of eczematous eruptions, patch testing of materials for consumer use, etc., pre-employment patch testing. This article<sup>133,134</sup> is recommended to any one who wants to familiarize himself with the possibilities, applications, limitations and dangers of the patch test. For patients who are sensitive to adhesive tape, Lipman Cohen<sup>76</sup> recommends a zinc gelatin bandage, similar to the familiar Unna boot. This seems a rather complicated procedure. Many patients who are sensitive to ordinary adhesive tape, apparently tolerate Scotch tape. According to Keil<sup>68</sup> the chief value of the patch test with a potent poison ivy extract rests with the fact that a negative test excludes past and present hypersensitivity to poison ivy. A positive test is no proof that the dermatitis under consideration is caused by poison ivy on account of the high incidence of positive reactions in the normal adult population. However, Keil<sup>68</sup> believes the quantitative patch test is an important method of checking the value of treatment in this disease. Keil did not observe untoward effects from his patch test.

*Treatment.*—Intravenous injections of sodium thiosulfate in contact dermatitis again are recommended by Strickler.<sup>126</sup> He gives 5 injections at intervals from twenty-four to forty-eight hours. The use of thiamin as an adjunct in the control of pruritus is recommended by Pipes<sup>105</sup>; 100 mgms. are given subcutaneously daily for two or three days, followed by an oral maintenance dose of 50 to 75 milligrams, depending upon the course of the dermatitis. Calcium gluconate intravenously in acute cases of poison ivy dermatitis is recommended by Baird<sup>4</sup>; also by Epstein<sup>40</sup> who usually continues after one or two injections with oral medication (chlorocalcium, 2 teaspoons three or four times a day). Goldman<sup>52</sup> considers oral poison ivy therapy as the best specific prophylactic agent, though it gives good but only transitory protection and produces a relatively high percentage of cutaneous reactions. Goldman states that the percentage of reactions may be reduced by careful individualization. O'Leary<sup>98</sup> warns against the therapeutic use of poison ivy extracts. Although some patients tolerate well injections of poison ivy antigen, its use on numerous occasions has been followed by a rapid spreading of the eruption to involve the entire body.

Overtreatment of skin diseases, especially in the acute state, is a frequent source of superimposed dermatitis. In many cases sensitivity to some medication is the cause.

Gaul<sup>49</sup> reports four such cases. However, as O'Leary<sup>98</sup> points out, an exacerbation of an existing dermatitis is not always due to sensitization. An ointment may not be tolerated because it is used during the improper stage, e.g., during the acute phase of a dermatitis.

With the increased and unrestricted use of powerful sensitizers such as the sulfonamides, the incidence of severe, disabling dermatitis from such and similar sources is appalling. There have been further warnings against the indiscriminate topical use of sulfonamides.<sup>1,5,39,104</sup> Abramowitz<sup>1</sup> states that sulfonamide drugs have no place in the treatment of uncomplicated eczematous dermatitis.

## MICROBIC ECZEMAS

(Fungous, Bacterial, Parasitic Eczemas)

*Epidermophytosis.*—The war has brought increased interest in fungus infections of the skin, chiefly due to the epidemics of superficial ringworm of the scalp in children and the frequent occurrence of dermatophytosis of the feet among soldiers and sailors. The allergist is especially interested in the latter. Weidman, Emmons, Hopkins and Lewis<sup>141</sup> present a comprehensive review on the present-day problems of dermatophytosis of the feet. The sometimes difficult problem of differentiating industrial dermatitis on the hands from trichophytids is dealt with by

Peck, Botvinick and Schwartz.<sup>101</sup> These authors found the following criteria practical in differential diagnosis:

1. An active fungus infection must be present before the diagnosis of trichophytid can be considered.
2. The trichophytin test should be positive.
3. If one is dealing with a trichophytid, it should not improve after a suitable removal from contact with industrial irritants.
4. Trichophytids prefer the palms, contact dermatitis the dorsa of the hands.
5. In a case where there is a positive scratch test as well as a positive trichophytin reaction and an active fungus infection, there is the possibility that one may be dealing with a combination of an "id" and an allergic contact dermatitis.

It is more and more recognized that not all cases of "athlete's foot" or of dermatitis of the toes are fungus infections. Hopkins<sup>63</sup> concludes that some of these nonmycotic lesions were due to infection by or sensitization to staphylococcus aureus, or to shoe polish, antiseptics and similar sensitizing substances. Hypostasis and trauma account for other groups of these disturbances of the feet.

The difficulties frequently encountered in establishing the diagnosis of a fungus infection in an eczematoid eruption are not fully appreciated. It is often impossible to demonstrate fungi either microscopically or by culture. Sometimes definite proof can be given only after several months or even years of observation and careful search for a focus. Eventually one may find a new primary blister, especially on the soles, that may yield fungi and clinch the diagnosis. On the other hand, there are many sources of error in the microscopical and cultural diagnosis of fungi. Elastic fibers and other threadlike particles are often mistaken for mycelia by the less experienced examiner. The so-called "mosaic fungi" are easily and frequently mistaken for real fungi. It is practically impossible to prove a diagnosis of epidermophytosis by the finding of spores alone. Cultural methods are also a source of errors. Saprophytes may be mistaken for pathogenic fungi, even by experienced observers. C. W. Emmons<sup>34</sup>, principal mycologist of the U. S. Public Health Service, calls attention to the misuse of the name "*Trichophyton rosaceum*." Of 12 fungi received from various laboratories not one represented this fungus. Ten were strains of *fusarium*, a saprophyte that has never been demonstrated to cause trichophytosis, one was a basidiomycete and one a strain of *trichophyton mentagrophytes*. This fungus, the principal source of epidermophytosis of the feet, is better known to the allergist and dermatologist as *trichophyton gypsum* or its variety, *trichophyton interdigitale*.

Treatment of epidermophytosis is still very unsatisfactory. That goes both for the plain fungus infections and for the eczematoid forms. While it is usually possible to achieve substantial symptomatic relief, permanent cures are probably rare, except in those hyperacute cases that lead to generalized exfoliative "ids." In these instances apparently the fungi are cast away by the exfoliation, and reinfection is prevented by the high degree of allergy. There is little doubt that many milder cases of epidermophytosis could be cured if more patients would muster enough patience to carry on regular treatment for periods of many months after the clinical signs have subsided. Any new method of treatment of epidermophytosis deserves interest. Keeney and Broyles<sup>67</sup> used sodium propionate in fungus infections of the feet and groins. Sodium propionate is fungistatic for common pathogens. The authors had good results in 55 midshipmen with sodium propionate as a 10 per cent ointment and as powder. However there were some recurrences because some of the men were careless. Contact dermatitis from sodium propionate was observed only once. Soaking of the patients' cotton hose with copper sulfate or copper acetate gave good results in epidermophytosis of the feet in experiments carried out by Crittenden and Joiner.<sup>21</sup> The skin of six patients appeared normal,

11 were improved, 1 became worse. Treatment lasted from one and a half to ten months. Lewis and Morginson<sup>75</sup> recommend ethyl chloride spray for the treatment of trichophytosis. Distinct frosting of the skin is produced. This treatment does not lead to a cure but may be used especially in the vesicular stage because it causes vesicles and pustules to subside and leads to drying of the skin and healing of denuded areas. Weidman and Glass<sup>142</sup> found 10 per cent boric acid in talcum as well as cresatin highly successful in epidermophytosis of the feet. The phenol-camphor treatment of dermatophytosis—a rather controversial subject a few years ago—is again fully endorsed by Phillips.<sup>103</sup> He treated 230 lesions of microscopically confirmed ringworm of the feet, groins and axilla. Phillips' report is rather optimistic. All cases were cured with the pheno-camphor mixture within an average of 4.3 to 4.9 days; the longest took thirteen days. In the control series, Whitefield's ointment with the addition of 0.5 per cent dithronol was used, and with this method, too, all cases were cured within an average of 5.5 to 6.1 days.

The value of trichophyton and oidomycin injections in eczematoid fungus infections of feet and hands is still under discussion. The reviewer has no doubts as to its efficacy in certain cases, but we are far from knowing which cases to select and what dosage to use. Saletta<sup>114</sup> reports very good results in triphophyton dermatitis if the patient is interested enough to continue over a long period of time. Schonwald<sup>116</sup> considers hyposensitization with a mixed trichophytin, the most important feature in the treatment of dermatophytosis. Ayres<sup>3</sup> points to the numerous reports of disabilities from vesicular dermatitis of hands and feet (pompholyx or dyshidrosis) in the armed forces. Heat and sweat may cause severe exacerbations of latent infections. Secondary "id" reactions on the hands, secondary pyodermas, etc., may still further complicate the picture. The cardinal rule in the treatment of such conditions—according to Ayres—is to avoid irritation from overzealous treatment. Very acute cases should be treated first by continuous wet dressings of saturated solution of boric acid or Alibour solution:

R: Copper sulfate	1.6
Zinc sulfate	5.6
Sat. sol. camphor water ad.	240.00

S. Dilute 2 tablespoons to 1 glass of water, and apply as wet dressings.

Blisters should, in addition, be opened and painted with 2 per cent aqueous solution of gentian violet. Combes<sup>18</sup> recommends the use of coal tar in eczematoid dermatophytosis of the feet and the hands.

*Moniliasis*.—Intertrigo is a form of microbic eczema of the folds of the skin. Maceration of the tissue is a major contributing factor. The most common causative organisms are streptococcus, staphylococcus, trichophytions, epidermophytions and, last but not least, monilia. The most favored local remedies in intertriginous moniliasis—according to Bechet<sup>7</sup>—are 1 to 2 per cent aqueous solutions of gentian violet, silver nitrate, ammoniated mercury ointment, 40 per cent sulfur paste, 5 per cent chrysarobin. To the reviewer, vioform has proved itself as rather effective in this condition. A 2 per cent suspension of the following composition can be used in most any except the acute cases:

Vioform	0.6
Ichthyol	1.0
Ether	
Alcohol aa ad	30.0

In the later stages 1 to 3 per cent vioform in vaseline is often helpful. Sulzberger<sup>130</sup> states that there are few infections of the skin in which the role of systemic derangements is as apparent as it is in certain cases of so-called moniliasis.

## PROGRESS IN ALLERGY

Diabetes, obesity, vitamin deficiencies and other general disturbances can be proved to be determining factors in certain cases. The reviewer agrees fully with this statement. In his experience the most efficient systemic medication in this condition consists of large amounts of vitamin B-complex. Where oral medication is not successful, it should be combined with parenteral therapy with crude liver extract.

*Bacterial Eczemas.*—Infectious eczematoid dermatitis due to bacterial sensitization, so common and troublesome, continues to be neglected in the literature. It is the opinion of Lane and his co-workers<sup>72</sup> that many of the dermatoses of the hands which are being called dermatomycosis, dermatophytid, contact dermatitis, housewives' eczema, dermatitis due to soap, neurodermite, nummular eczema or bacterid, should be more correctly called infectious eczematoid dermatitis. Systemic administration of sulfonamide drugs and injections of staphylococcus toxoid have been occasionally satisfactory; elimination of a focal infection occasionally proved helpful. In some cases of infectious eczematoid dermatitis, penicillin is of great help. Cohen and Pfaff<sup>17</sup>, using penicillin both parenterally and as an ointment, containing 100,000 Oxford units in 30 gms. of ointment base, found this method beneficial in the treatment of infectious eczematoid dermatitis, moniliasis and dermatophytosis with streptococcic pyoderma.

Sulfonamides are widely used in the treatment of bacterial eczemas. Several authors<sup>39,104</sup> warn of the special danger of sensitization in patients suffering from infectious eczematoid dermatitis. According to Pillsbury<sup>104</sup> sensitivity to sulfonamides, especially sulfathiazole, may be easily induced by local application in chronic dermatoses in which there is an element of sensitivity, particularly to pyogenic bacteria. This marked ease of sensitization offers a serious contra-indication to local sulfonamide therapy in such cases. Yet the use of these drugs externally as well as internally is sometimes especially helpful in infectious eczematoid dermatitis.<sup>39</sup> To reduce the risks of external sulfonamide therapy, Epstein<sup>39</sup> presents the following six suggestions:

1. Sulfonamide ointments, lotions and powders should be used only with proper indications.
2. Physicians should become aware of the special danger of sensitization in infectious dermatitis.
3. Sulfanilamide should be substituted for sulfathiazole.
4. The patient should be informed that he has become sensitive to a sulfonamide.
5. Penicillin should be used in sulfonamide-sensitive patients.
6. The public should be enlightened about the risks connected with the use of sulfonamides.

*Seborrheic Dermatitis.*—This condition is also—at least to some extent—an infectious eczema. Experimental data presented by Simon<sup>124</sup> suggests that the human dander allergen is present also in scales of seborrheic dermatitis but absent in numerous other scales and other materials. Frank believes that the allergen is not a constituent of stratified squamous epidermis; nor does he believe that it has its origin in accidental contamination of dander with suspended dust particles from the air. It is possible that the allergen may be of microbic origin. Frank thinks that his findings may be of importance for the study of seborrheic dermatitis. Scott<sup>121</sup> lists among seborrheic eruptions dry and greasy dandruff, follicular seborrheides of the scalp, face, chest and back, axillae, groins and also of the limbs. In Scott's opinion, the seborrheic diathesis is due partly to dietetic indiscretions and partly to a hormonal deficiency. The seborrheic state is a prediabetic state, accompanied by retention of fluids in the tissues. Scott believes that in seborrheic subjects, androgen is in excess in the blood over estrone. The various or-

ganisms found in seborrheic eruptions are *not* the cause. These eruptions can be complicated by superadded coccal or mycotic infections, which are too often thought to constitute the whole of the disease requiring treatment. This consists in dietetic and hygienic measures such as frequent baths, ultraviolet treatment, exposure of the skin to the air, especially cool air. He describes a mixed diet with no excess of fats and carbohydrates. Scott gives Stilbestrol for more severe cases. For the mild hypochromic anemia, found generally in long-standing cases, he prescribed iron and arsenic. As far as local treatment is concerned he warns against unsuitable, ill-timed, irritating local treatments. The first duty is to give the skin a rest. For the purely seborrheic or very little infected eruptions the following ointment is recommended: 2 per cent precipitated sulfur, 4 per cent salicylic acid, 1 per cent resorcin in equal parts of oleum cocois and vaseline alba. In case of coccal infection 2 per cent ammoniated mercury, 6 per cent pix liquida in the same base. These ointments should be applied sparingly and not longer than a few weeks to prevent sensitization. Desensitization by intracutaneous injections of bacterial antigens is definitely useful. While the reviewer does not subscribe to all of Scott's assumptions, his therapeutic approach to seborrheic dermatitis coincides in many instances with that of Scott. Iron is a very helpful adjunct in many cases of seborrheic dermatitis. Sulfur is widely used in seborrheic dermatitis. Downing, Ohmart and Stoklossa<sup>30</sup> recommend a comparatively new suspending agent, methyl cellulose, for improving suspensions of sulfur. Their formula for a smooth, creamy sulfur lotion is as follows: (gm. or c.c.)

Precipitated sulfur	10.0
Spirit of camphor	10.0
Alcohol	80.00
Solution of methyl cellulose, 2%	30.00
Rose water to make	240.00

*Other Parasitic Eczemas.*—It appears proper to review here eczemas and dermatitis from animal parasites. "Cheese itch," a dermatitis caused by mites, is more common than might be expected by the relatively few reports published. This becomes apparent from a discussion of this subject in the Royal Society of Medicine.<sup>108</sup> Prosser Thomas<sup>138</sup> has probably seen at least 200 cases. The mite is *Tyroglyphus longior*, and found in the coverings of moldy cheese. Whether the mites produce a toxin has not been settled, but made improbable by Forman's<sup>45</sup> experiments. He found positive patch tests to cheese "dust" in two patients, but had a negative result on his own skin. Dermatitis from grain mites (*tyroglyphidae*) in two men handling straw packing material is reported by Thomas S. Saunders.<sup>115</sup> The eruption occurred as a papular excoriated dermatitis of the wrists in one instance, and of arms and face in the other. Unlike *acarus scabiei*, members of the *tyroglyphidae* family do not burrow into the skin. Saunders believes that such eruptions are more common than is realized. "Grocer's itch" is a dermatitis caused by handling dried fruits. According to Schwartz<sup>119</sup> mites are sometimes found in dried dates, prunes, figs, apples and pears. Animal origin other than scabies may be the cause of pruritic, papular eruptions more often than suspected. Russel C. Anderson<sup>2b</sup> reports a case of such a dermatitis caused by the tropical rat mite, *Liponyssus Bacoti* Hirst. Mites were found on the patient's body and on the kitchen wall in the vicinity of a cupboard that was infested with rats.

#### OTHER FORMS OF ECZEMA

Under this heading eczemas of unknown origin will be reviewed as well as those allergic eczemas that do not fit in the other three groups.

*Nummular Eczema.*—According to P. Gross<sup>58</sup> nummular eczema is a recalcitrant dermatosis consisting of coin-shaped patches of erythematous, vesicular eczema with varying degrees of edema and exudation. The sites of predilection are the backs

of the hands and fingers and the extensor surface of the extremities. The shoulders and the face are occasionally involved. The psychosomatic-minded physician will easily find psychogenic and neurogenic factors. Gross<sup>58</sup> prefers to look for the conditioning factors of Vitamin A deficiency, and such search is rewarded by the finding of biliary tract disease, hypothyroidism or hyperthyroidism.

The value of injections of crude liver extract in treating various forms of eczema, is stressed again by P. Gross.<sup>58</sup> At the present stage of our knowledge the vitamin B complex, as represented by crude liver extract, contains a number of factors which either have not been identified or, like folic acid, have been unavailable for clinical experimentation. One can therefore not expect to duplicate the results obtainable by liver extract injections through the use of single vitamins. Animal experiments by Sullivan and Evans<sup>129</sup> may throw some light on the role of vitamin B avitaminosis in eczemas. These investigators produced generalized cutaneous lesions in rats superimposing vitamin A deficiency on vitamin B complex (other than thiamine) deficiency.

The eruption consisted of numerous small scattered squamous plaques. Microscopic examination showed atrophy of the epidermis and appendages, dilatation of atrophic hair-follicles and excessive hyperkeratinization.

Numerous cases of eczemas are caused by a variety of factors. Templeton<sup>137</sup> reminds us that many times the clinical pictures of epidermal sensitization and dermal sensitization merge when both epidermis and the dermis are sensitized. Templeton discusses several such cases. Probably the most frequently seen examples are from sensitization to drugs. As an example of epidermal and dermal sensitization from plants, Templeton reports urticarial reactions following parenteral or oral administration of poison oak extract in patients suffering from poison oak contact dermatitis (epidermitis). Epidermal and dermal sensitization to foods are relatively rare. A case of ephedrine sensitivity with epidermal sensitivity is presented by Lewis.<sup>74</sup> A contact dermatitis—like bullous dermatitis of hands and feet—followed the intranasal application of ephedrine. A patch test with ephedrine hydrochloride in a dilution of 1:1000 gave a strong blistering reaction with a slight exacerbation of previously affected sites. An intradermal injection of 0.1 c.c. of a 1:1000 solution of ephedrine produced an immediate erythematous urticarial reaction.

Perhaps the most complex eczema is eczema of the hands. This is brought out again by a paper about this condition by Lane, Rockwood, Sawyer, and Bland<sup>72</sup>, and its discussion by several dermatologists. Out of a series of 475 cases of "eczematoid" dermatoses of the hands, the diagnosis of dermatomycosis, dermatophytid, contact dermatitis or soap dermatitis could be confirmed only in very few of the cases. In a very large number the cause is not known. These authors present the following hypothesis: There are various inciting factors. There may be several complicating factors: excessive soap and water, vasomotor instability, trauma, menstruation, hot or cold weather or focus of infection. There occurs an alteration of host-bacteria relationship. There may be a superficial bacterial invasion of the skin, with or without sensitization. The inciting factor may be removed but the eruption may persist as infectious eczematoid dermatitis, a recurrent superficial invasion of the skin by bacteria of low virulence which relapses when the host-bacteria relationship is disturbed by one or more of the aforementioned complicating factors. Sulzberger<sup>131</sup> suggests among other etiologic factors the possibility of infections with the virus of herpes simplex, especially in relation to nummular eczema.

#### URTICARIA

Herrmann, Sulzberger and Baer<sup>60</sup> report several cases of contact urticaria. The well-known fact that some children develop an immediate urticarial eruption is

exemplified by two cases where contact with silk and wool respectively produced an immediate urticarial reaction. A scratch test with silk was strongly positive in this case. They emphasize that by no means all silk or wool garments produced these transepidermal reactions. Only certain of the mother's silk clothes produced hives through contact with the skin. They report other instances in bakers and bartenders where swelling and itching of the hands occurred within a few minutes after contact with citrus fruits or wheat, respectively. Gutmann<sup>59</sup> reports two cases of urticaria and angioneurotic edema from Palestine, which were caused by chlorinated drinking water. This etiologic factor seems well established in Gutmann's cases. A case of severe urticaria following immediately the intravenous use of pooled human plasma is reported by Dickstein.<sup>25</sup> By a series of ingenious experiments, Dickstein found that the reaction was due to the fact that the patient was allergic to milk, beef and lamb and that those allergens were present in the pooled plasma. Urticaria caused by sensitivity to mercury used as dental fillings is reported by Marcow.<sup>82</sup> The urticaria started after a visit to the dentist. Removal of each filling was followed by a flare-up; complete relief occurred after all silver fillings had been removed. A contact test with mercury was immediately followed by a local urticarial reaction. Urticaria is thought to be caused in most instances by foods or drugs. Derbes and Engelhardt<sup>24</sup> report two cases which they attribute to inhalants; in one instance to ragweed pollens, in the other to fumes of fresh paint. Urticaria may be caused by still other factors. D'Ingianni<sup>26</sup> discusses the pathogenesis and etiology of urticaria caused by caterpillars. The lesions are produced by the caterpillar hair, the toxin glands or by both. According to Leon Goldman<sup>53</sup> urticaria and dermographism are seen occasionally in patients with scabies, especially in easily excitable and apprehensive persons.

*Treatment.*—S. N. Saletta<sup>113</sup> reports good results from histamine especially in food urticaria and also in a case of severe dermatographia. Toomey, Kreite and Epstein<sup>139</sup> conclude from their well-controlled clinical experiments that there is no indication that histaminase (torantil) prevents or ameliorates the urticaria of serum sickness. In Eger and Stone's<sup>32</sup> thirty-one cases oral administration of twenty units of histaminase every three hours also failed to shorten the course of the symptoms of serum sickness. Rather encouraging results with the use of hapamine in the treatment of several cases of urticaria are reported by Edrington.<sup>31</sup> Successful treatment of persisting urticaria with synthetic vitamin K is reported by Black.<sup>10</sup> Two milligrams three times daily before meals was adopted as the routine dosage, duration of the treatment varied from one to four weeks. Treatment was carried out only in those cases that did not respond to the usual allergic management. In many instances lesions failed to appear after two days of treatment. The best results were observed in those cases that had a prolonged prothrombin time.

The psychosomatic aspect in urticaria is stressed by Wright.<sup>143</sup> An analysis of twenty-five cases of chronic urticaria revealed that seventeen of them (70 per cent) had some definite shock, worry or nervous exhaustion preceding or accompanying the onset of their illness. Wright reminds us that the allergic threshold may be raised or lowered by emotional tension.

#### DRUG ERUPTIONS

Drugs are capable of causing a great variety of skin manifestations. Drug eruptions may imitate—so to speak—nearly every other skin disease. To give a few examples, aspirin erythema may resemble perfectly the scarlet fever rash, sulfathiazole may produce erythema nodosum-like eruptions; the bullous lesions from barbiturates at times are indistinguishable from pemphigus. The granulomas of bromoderma resemble malignancies, syphilitic gummas, or fungous granulomas and have been mistaken for them, sometimes with unpleasant consequences for the pa-



tient (Netherton<sup>97</sup>). In recent years the medical profession has become more aware of the high incidence of these drug eruptions, largely due to the numerous, mostly allergic toxicodermas accompanying the use of sulfonamides. The importance of these often severe, and not too infrequently fatal, reactions cannot be overemphasized. For these reasons it seems justified to add to this review a chapter on drug eruptions even if there is some overlapping with the review on drugs by E. A. Brown<sup>13</sup> and the chapters on contact dermatitis and urticaria of this review.

*Sulfonamides.*—The greatest interest still is commanded by the eruptions from sulfonamides.<sup>66</sup> Under the title "Sensitivity to sulfadiazine resembling acute disseminated lupus erythematosus," Hoffman reports a case of severe sensitivity from sulfadiazine. Another case of fatal bullous dermatitis following the use of sulfadiazine medication is reported by Dardinski<sup>22</sup> under the title "Erythema multiforme bullosum." This case is similar to that previously reported by Greenberg and Messer.<sup>56</sup> Watchfulness for drug sensitivity becomes still more important with the increased use of sulfonamides for chemoprophylaxis. According to Morgan and Turner<sup>95</sup> disasters may follow the therapeutic administration of sulfonamides in persons who had received prophylactic doses when manifestations of sensitivity to the drug were erroneously diagnosed as conditions for which sulfonamide therapy was believed indicated. Among the mistakes listed were scarlatiniform rashes diagnosed as scarlet fever, tonsillar and pharyngeal lesions diagnosed as acute streptococcal infection which were actually manifestations of agranulocytosis. Reactions of extreme severity occurred in patients with sulfonamide agranulocytosis by transfusions from donors who were taking prophylactic doses of sulfadiazine. Morgan and Turner stress that disastrous consequences of sulfonamide therapy can be eliminated only when physicians acquire the fixed habit of never prescribing the drugs until it is certain that the condition under treatment does not represent, even in part, a manifestation of sensitivity to sulfonamides. In every instance, fever and skin rash should be first suspected as due to sulfonamides.

There are quite a few reports about sulfonamide eruptions following external application of the drug.<sup>43,66,135,136,102</sup> Of 2,280 patients who were admitted to the dermatologic division of a military hospital during a period of six months, Tate and Klorfajn<sup>135,136</sup> found fifty-five cases of sulfonamide dermatitis produced by local application of the drug. Four of these cases also manifested symptoms of photosensitivity. All the cutaneous lesions were of an eczematous nature. The interval between the start of the sulfonamide application and the onset of the dermatitis, in eleven cases was from four to seven days; in ten, from seven to fourteen days; and in nine, more than fourteen days. No noticeable constitutional predisposition to sensitization was observed. Positive patch test reactions were obtained which were stronger after slight scarification of the skin. In some cases, the positive patch test was limited to the dermatitis area. The sensitivity persisted as long as eighteen months in some patients. These authors conclude that the use of sulfa drugs in topical therapy is unwarranted, unless life is endangered or unless the results of healing would otherwise lead to a deformity.

Fisher<sup>43</sup> reviews one hundred cases of sulfonamide dermatitis following local applications. Four of eight patients tested by oral administration of the drug had generalized reactions. Tate and Klorfajn<sup>135</sup> report attempts at oral desensitization in thirty patients suffering from sulfonamide dermatitis. Reactions during desensitization included fever, aggravation of dermatitis, loss of consciousness in one case. In view of the fact that penicillin now is readily available, it seems doubtful whether such a dangerous procedure is still justified. Peterkin<sup>102</sup> reports sixty-five cases of sunlight eruptions due to external application of sulfanilamide. In sixty-one of these cases, sulfanilamide powder was the first sulfonamide drug to be applied. Of 200 other cases that were treated with a 5 per cent sulfathiazole ointment, only one developed a sunlight eruption, although their skin was freely

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exposed to light. This observation leads Peterkin to the suggestion that sulfonamide sunlight eruptions are almost invariably preceded by application of sulfonamide powder and that the patient becomes sensitized to the drug by its inhalation. A less hypothetical explanation for the author's observation may be given by the fact that sulfanilamide is a photosensitizer<sup>11,36</sup>, but sulfathiazole is not. Allergic light sensitivity may be produced by both, but apparently more rarely by sulfathiazole. An interesting form of drug sensitivity are the so-called fixed drug eruptions. They consist usually of single lesions recurring almost always at the same place. Favorite locations of fixed drug eruptions are the fingers, forearms, and penis. They are frequently characterized by pigmentation. Freeman<sup>46</sup> reports the first case of such an eruption caused by sulfadiazine. The patient showed a slightly raised, bright purplish-red eruption, about the size of a quarter, on the dorsum of the right thumb. He gave a history of having had a similar eruption in the same area about three months previously. The last eruption had followed the second dose of 1 Gm. of sulfadiazine, which was taken for rheumatoid arthritis. Six weeks later, within six hours after having taken 2 Gm. of sulfadiazine, the same eruption recurred. Patch tests with sulfadiazine were negative. Recurrences of the fixed eruption also followed the ingestion of sulfamerazine. The existence of these fixed drug eruptions is not generally recognized. The allergist and practitioner should become more familiar with these lesions. Their recognition has an added importance as sometimes these eruptions turn into generalized drug eruptions if the causing agent is not eliminated.

As a rule, scratch and intradermal tests are negative in drug eruptions. An intradermal test for the recognition of hypersensitivity to sulfonamide drugs is described by Leftwich.<sup>73</sup> Sera from patients receiving sulfonamide therapy from one to fifteen days were used for cutaneous testing for hypersensitivity to these drugs. About 0.05 c.c. of serum was injected intracutaneously on the flexor surface of the arm. The control serum produced an initial wheal of 6 to 7 mm. in diameter, which increased to from 1 to 2 cm. with an erythema up to 20 mm. A positive reaction consisted of an initial wheal similar to that of the control wheal, which increased immediately to from 12 to 18 mm. with pseudopod formation. The accompanying erythema measured 30 to 40 mm. The reaction reached its maximum within fifteen minutes. Delayed reactions were not observed. Tests were made on thirty patients, of whom eighteen were clinically sensitive only to sulfadiazine, and four only to sulfamerazine. A positive cutaneous reaction was reported in twenty-eight (90 per cent). The testing serum was found to be highly specific. Freezing and preservation of the serum in the frozen state for two months did not affect its reaction-producing properties. Heating at 60° C. for three minutes destroyed these properties. Sera obtained from patients receiving the drug for less than five days did not produce a positive reaction. The drug level of the serum did not appear to have any effect on its reaction-producing properties. The cutaneous reaction could be elicited as soon as signs and symptoms of the sensitivity appeared and were obtained in two patients, one and five years after the occurrence of the dermatitis. The author suggests that the sensitizing antigen may be a sulfonamide-plasma-protein combination, the sulfonamide being a hapten.

*Penicillin.*—Penicillin still holds the record of low toxicity although reports of sensitivity, especially of the skin, are on the increase. As far as I can see, no accidents of very serious nature have been reported as yet. Experimental evidence by Rake, McKee, Hamre and Houck<sup>121</sup> bears out the low toxicity of penicillin. They found that penicillin, even in impure form, is many times less toxic for animals than any other well-known antibiotic substance. The reports of penicillin intolerance indicate that penicillin produces different forms of sensitivity, contact type, as well as urticarial eruptions. Also combinations of different types in the same patient as demonstrated by Morris and Downing's case<sup>66</sup>, a bullous dermatitis

from penicillin in a man who had received 1,000,000 units. The dermatitis started with itching and erythema, followed by edema and bullous eruptions. The patient also developed multiple wheals of various sizes. Urticarial reactions to penicillin have been described by Lyons<sup>81</sup> as occurring in twelve, or 5.7 per cent of 209 cases treated in army hospitals. Crip<sup>20</sup> reports a case of severe massive generalized urticaria that developed in a soldier immediately following his second course of penicillin. The urticaria would develop immediately on receiving the injection and was continuous and universal during the time the penicillin was given daily. It disappeared when penicillin was discontinued a week later. In this case, the patient gave a positive intradermal test with a penicillin dilution of 1:100, which did not produce any reaction in four controls. There was further a definite precipitation in blood serum dilutions up to 100. Passive transfer also was positive. The patient did not show any reaction to a test with penicillium extract. Crip believes that penicillin allergy is probably unrelated to sensitivity to penicillium spores. Another case of giant urticaria after intramuscular injections of penicillin is reported by Barker.<sup>6</sup> Scratch and intradermal tests produced an urticarial wheal which persisted for twenty-four hours; tests using autoclaved solutions were negative. The significance of positive whealing reactions from penicillin without proper controls appears doubtful from Welch and Rostenberg's<sup>140</sup> experience. They found that most commercial penicillin sodium is a mild primary irritant when injected intracutaneously, producing within one to two hours erythema and edema. Crystalline penicillin, however, has no primary irritating properties. Contact dermatitis from penicillin eye drops is reported by Selinger.<sup>122</sup> Noteworthy in this case was the absence of any conjunctival irritation in spite of the rather pronounced dermatitis of the lids. Contact dermatitis from penicillin due to professional or industrial exposure has been reviewed in the chapter on contact dermatitis (epidermitis).

Welch and Rostenberg<sup>140</sup> add one more form of penicillin sensitivity to the reports of positive patch and whealing reactions. In a man who had worked with various molds for a period of fifteen years, but who had never received penicillin, they discovered a tuberculin type of reaction both to crystalline penicillin sodium and to several commercial brands. The test person developed an infiltrated erythematous and vesicular lesion that started about six hours after the injection and reached its maximum between 48 and 96 hours. Graves, Carpenter, and Unangst<sup>54</sup> report two cases of vesicular eruptions of the hands and feet respectively which followed injections of penicillin. In the first case the eruption recurred with each succeeding injection and produced also petechiae. The lesions disappeared when penicillin therapy was stopped. An intracutaneous test with penicillin showed a delayed positive reaction in 96 hours. The other patient developed a vesicular eruption of his hands within twenty-four hours after his first injection. He, like the first patient, had had a similar eruption previously. However, in this case the lesions subsided in spite of the continued penicillin therapy. The intracutaneous test with penicillin was negative. Trichophyton test was positive in this case as well as in the first one. The author suggests the following three possibilities: (1) The lesions may have been produced by an antigen common to both penicillin and trichophyton. (2) The bactericidal action of penicillin may have released toxins from these patients' fungus infection. (3) The eruptions may have been due to the penicillin or some impurities. It would seem that the first case was due to a sensitivity to the drug. The second case appears due to toxins liberated from a focus of infection by penicillin. This case demonstrates again that not all eruptions caused by drugs are caused by sensitivity. The fact is well known; one of the best examples perhaps is Milian's "Erythema of the ninth day," following arsenical treatment of early syphilis.

Potter and Whitacre<sup>107</sup> report a case of a severe generalized dermatitis with anemia from barbiturates (luminal plus amytal). It is well worth while to remind us ever

so often of the severe, sometimes fatal, eruptions from barbiturates. Luminal (phenobarbital) is perhaps the most beneficial sedative in all forms of eczemas, but perhaps also the most dangerous in regard to toxic eruptions. Thiouracil, used in the non-surgical therapy of thyrotoxicosis, is an unpredictably toxic drug. Among forty-three patients treated with it by Gargill and Lesses<sup>47</sup>, toxic reactions developed in eight, skin manifestations (urticaria, pruritus) in two of these cases. Garrilove and Bert<sup>48</sup> reported dermatitis from thiouracil in two cases. Localized, as well as severe generalized urticaria as manifestation of sensitivity to liver extract, is reported by McSorley and Davidson.<sup>55</sup> Nodular bromodermas are rather uncommon. According to Netherton<sup>97</sup>, a painful, nodular, papillomatous pustular lesion, not surrounded by acute cellulitis, should make us consider bromoderma. The most striking feature of this type is the high incidence of severe pain and tenderness of the lesions. Netherton reports four cases. The diagnosis is important because this condition may be mistaken for a fungus infection, syphilis or even a malignancy. Recognition of papillomatous bromoderma will prevent surgical interference to which these lesions are at times subjected.

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# \* *In Memoriam* \*

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## EDWIN J. BARNETT

Dr. Edwin J. Barnett of Spokane, Washington, an Active Fellow of the American College of Allergists, died suddenly as the result of coronary thrombosis, March 29, 1945, at his home.

He was born March 30, 1894, at Peoria, Illinois. He attended the medical school of the University of Illinois, from which he received his M.D. degree in 1916. Doctor Barnett later took postgraduate work in pediatrics at Harvard University Medical School. During the first world war he was in France, attached to the hospital unit of Spokane doctors and was invited by the late Dr. Peter McCornack to come to Spokane as his associate.

Doctor Barnett was a member of the American Academy of Pediatrics, the American Medical Association, Washington State Medical Society, Spokane County Medical Society, North Pacific Pediatric Society, Nu Sigma Nu Medical Fraternity and a diplomate of the American Board of Pediatrics. He specialized exclusively in pediatrics with special work being devoted to allergy. He was the discoverer of tick paralysis, concerning which he presented a paper at a recent meeting of the American Medical Association at Atlantic City, New Jersey.

At the request of a group of business associates and close friends of Doctor Barnett, the Spokane County Medical Society has been asked to supervise the formation of a memorial fund to honor him and to be used in establishing a suitable memorial to him at one of the hospitals.

Doctor Barnett is survived by his wife, a daughter and a son.

The College has lost a valuable member in the passing of Dr. Edwin J. Barnett.

FRED W. WITTICH

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## MORTON GUZY

Dr. Morton Guzy, an Active Fellow of the College, died July 20, 1944, at Bridgeton, New Jersey, where he had practiced medicine since 1941. Death was caused by a heart ailment. He was born in New York City, February 17, 1915.

He was graduated from the Medical College of Virginia in 1939 and served his internship at Philadelphia Jewish Hospital. Doctor Guzy was a member of the staffs of Philadelphia Jewish Hospital, St. Luke's Children's and Medical Center and the Bridgeton Hospital. He was a member of the American Medical Association, New Jersey State Medical Society and Cumberland County Medical Society. He was also a courtesy member of the Philadelphia County Medical Society and Alumni Society Medical College of Virginia. Doctor Guzy was affiliated with Phi Beta Kappa and Chi Beta Phi fraternal organizations.

His interest in allergy included all types of the specialty, particularly the pollen variety, and he had engaged in special work in allergy with Dr. Erich Urbach at the Philadelphia Jewish Hospital.

Doctor Guzy was an enthusiastic member of the College. His untimely death is a loss to our organization.

FRED W. WITTICH

# Questions and Answers

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What is known about cocoa butter sensitivity?

M.D., Pennsylvania.

Cocoa butter has been listed as causing irritation in persons working in cocoa butter factories. It has been used extensively in pomades, salves, cold creams, vanishing creams and fine soaps, and is a base for ointments and for suppositories. Sensitivity is described in the book by Prosser R. White, "The Dermatoses or Occupational Infections of the Skin," 4th edition (London), H. K. Lewis and Company, 1934, page 273. This knowledge would indicate that the patient requires patch testing with the material at fault, although it should be understood that the medication which the cocoa butter carries is more often the cause of dermatitis than is the vehicle itself.

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What procedures are used to distinguish between chronic dyspnea of allergic origin and cardiac failure where the clinical features are vague?

M.D., Minnesota.

In general, the differentiation between the dyspnea of bronchial asthma and that due to cardiac disease is not difficult. In two groups of cases, however, the distinction may be at once difficult and highly important from the standpoint of therapy.

The first of these, paroxysmal nocturnal dyspnea due to acute left ventricular failure, may simulate exactly the paroxysm of bronchial asthma. It may be brief, unaccompanied by bloody sputum, and may come without the warning of previous exertional dyspnea. However, there are three important differences: (1) There is usually evidence of an increased load upon the left ventricle, either hypertension or an aortic valvular defect; (2) There is clinical and/or x-ray evidence of left ventricular enlargement and/or electrocardiographic evidence of myocardial damage; and (3) The arm-to-tongue circulation time is practically always prolonged, often two or three times normal. This latter value, measured by any one of a number of methods (the saccharin method of Fishberg, Hitzig, and King<sup>1</sup> is quite satisfactory) is an extremely valuable diagnostic aid. It is always normal in *uncomplicated* bronchial asthma.

The second group of cases presents a more complicated problem. These are the patients with bronchial asthma of long duration with obstructive emphysema of greater or less degree who begin to exhibit exertional dyspnea, cyanosis, engorgement of the systemic veins, and possibly edema. Ordinarily these symptoms mean heart failure, and since it is well known that emphysema results in right ventricular strain and occasionally frank heart failure, it is only natural that the appearance of these symptoms in an asthmatic should be looked upon as evidence of cardiac weakness. This in turn inevitably brings about a cardiac regime which adds further complications in the life of the unhappy asthmatic without producing any substantial benefits.

It is important to realize that *all* the above symptoms may be present in the emphysematous asthmatic *without* demonstrable evidence of heart weakness and due solely to pulmonary causes (loss of lung elasticity, decreased vital capacity, increased residual air anoxemia, dilatation of cervical veins due to repeated paroxysms of asthma, increased intrapleural pressure, and compression of the inferior vena cava due to pressure from a low diaphragm).<sup>2</sup>



- Since heart failure does occur as a result of emphysema and is manifested only by an *increase* in the dyspnea, cyanosis, venous engorgement, and edema, how can one determine when the cardiac element begins to predominate?

X-ray evidence of right ventricular enlargement is convincing but may be borderline for long periods. Much more valuable is the determination of the venous pressure. Like circulation time determinations, it is a simple procedure; and when performed with reasonable care as to details<sup>3</sup>, will afford an excellent measurement of right heart efficiency. It is normal or only slightly elevated in emphysema uncomplicated by heart failure<sup>4</sup> and considerably elevated in right heart failure.

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**What are some of the failures in the treatment of hay fever attributed to, and how are they to be avoided?**

M.D., Missouri

The treatment of hay fever consists of other important factors besides hyposensitization. Failures are, as in any scientific procedure, frequently the result of untested assumptions, inadequate control measures, careless care of extracts and apparatus, and faulty conclusions not based on facts.

It is better to treat a few patients adequately, rather than treat a large "assembly line" inadequately. Among the ways of going astray are:

1. Failure to individualize the patient. There is a tendency of the less experienced to apply the same dosage schedule regardless of the physical condition of the patient or to attempt to adopt a particular method of specific desensitization.

2. Injudicious selection of the three general methods of hyposensitization treatment, and failure to base the dosage on the susceptibility of the patient. In some instances, two or more methods may be used in the same patient. Some patients obtain very satisfactory results on preseasonal treatment alone each year. Another group having received preseasonal therapy in the properly prescribed manner and having reached the top doses just prior to the season will not receive adequate relief. Treatment should be continued coseasonally on a "primary" coseasonal schedule just as though the patient had not received preseasonal therapy. This is given in 10 or 20 pollen units (0.1 c.c. of 1:5,000 dilution, equals 20 units). The correct initial dose is the smallest amount which gives relief. If 20 units relieve symptoms, the same dose is given daily. Adequate dosage gives 75 per cent relief for one to two days. It is rarely necessary to give more than 80 units (0.4 c.c. of 1:5,000) and the interval lengthened to three days. If a patient has symptoms at the time of injections, 0.3 c.c. of epinephrine 1:1,000, or a mixture of equal parts of epinephrine 1:1,000 and three per cent aqueous ephedrine administered with the pollen gives relief. Some patients after receiving treatment by these two methods may still have symptoms. Then, irrational as it may appear, daily injections of 1:5,000 as well as concomitant biweekly injections of 1:50 may be indicated in doses of one-half or less of the preseasonal top dose. The biweekly injections serve as a maintenance dose to prevent loss of what tolerance the patient has received while the small daily injections are given for present relief of symptoms.

Some patients are fortunate to receive adequate relief with six to twelve injections during the season, by following the primary coseasonal schedule. When a patient reports two or three weeks before the season, it is best to advise primary

## QUESTIONS AND ANSWERS

coseasonal treatment or give a few preseasonal doses with no attempt to reach the proper top dose, and then follow with coseasonal treatment.

When a patient is away from home during the summer, coseasonal or perennial treatment may be tried. The latter method reduces the number of injections during the summer vacation. When relieved coseasonally and continuation with perennial treatment is desired, weekly injections are given following the season according to the preseasonal method, and when a maintenance dose is reached, the latter is repeated twice monthly throughout the year until about one month before the next season. The dose is then rapidly raised to the top dose with weekly injections.

3. Failure to consider family or genus specificity. Much accumulated evidence would indicate that although pollens which are biologically related show common antigenic properties, they are not completely identical for all pollens or for other members of the same family. When making a clinical application of this information, it is better to test with several different species among the pollen families, tribes, or genera. The best therapeutic results are obtained by including in the treatment extracts all of those species in proper proportion to which the individual is *actually exposed* during the period of his symptoms.

When dealing with unrelated pollens, such as ragweed and English plantain, or ragweed and the grasses, or trees and grasses, the top dose should be independent for all unrelated pollens and not represent a composite. The top dose required for grasses is usually less than that for weeds. Combined treatment with grasses and weeds are frequently very satisfactory.

4. The failure to recognize the importance of food and other inhalant allergens in pollenosis.

The symptoms of, at least, three-fourths of the patients clinically sensitive to pollens are also due to one or more foods or inhalants or both, which require avoidance measures for adequate treatment of the pollenosis. These offending foods may frequently be eaten out of season without causing symptoms. In some cases of pollenosis they are made comfortable without other measures than food restrictions and avoidance of other inhalant offenders. This has been found particularly true of seasonal asthma complicating pollenosis. All patients with seasonal hay fever should be routinely tested with the foods eaten most frequently as well as those foods not likely to be eaten except during the hay fever season, such as watermelon, cantaloupe, certain fruits, et cetera.

The intensity of the allergic stimulus would appear more important than the kind of stimulus, so concomitant, infective, contact, or physical allergy must be considered as influencing the symptoms.

5. Failure, as the result of placing entire dependence on direct skin tests, to determine the clinical pollen excitants when making an extract for hyposensitization. Positive skin reactions frequently occur with pollen which do not cause symptoms in the patient. A pollen giving a positive mucous membrane reaction is more often the cause of the patient's symptoms. When there is multiple sensitivity to pollens or a pollen occasionally gives a negative skin reaction which is strongly suspected as a clinical offender because it is toxic, and coincides with symptoms and atmospheric prevalence, the ophthalmic and nasal contact tests may respond. Passive transfer is considered most reliable with pollens and should be used where there are unsuitable skins (dermographia, et cetera).

6. Most constitutional reactions are due to carelessness. They may be produced by: Rapid forced injections deep into the muscle; failure to determine if the needle is in a blood vessel; failure to dilute concentrated solutions adequately or not including epinephrine when top doses are reached; failure to reduce the dose when a new or fresh lot of extract is substituted; failure to test the patient intradermally with low serial dilutions before determining the initial subcutaneous dose;

failure to caution the patient to not indulge in violent exercise immediately following the injection; failure to ask the patient if the last previous injection caused itching or a local reaction larger than a half dollar, or whether there was some nasal stuffiness or sneezing following the previous treatment; failure to reduce the dose if more than three weeks have elapsed since the previous dose; failure to impress the patient with the importance of receiving the injections regularly on schedule.

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*Effect of Ergotamine Tartrate and Neosynephrin hydrochloride on the Work Capacity of Human Muscle.* Kotalik, G. C., Maison, G. L., and Pfeiffer, Carl: Am. J. M. Sc., 206:503, 1943.

In an effort to determine whether the asthenia after the use of ergotamine tartrate was due to the drug or whether it was coexistent migraine phenomena that the drug was unable to eliminate, the authors used twelve subjects and the Maison ergograph to the point of fatigue to measure work capacity. No significant decrease in work output occurred after the intramuscular injection of ergotamine tartrate ( $\frac{1}{4}$  to  $\frac{3}{4}$  mg. dosage). There were few subjective symptoms. The work capacity was also tested after injection of 4 to 10 mg. neosynephrin hydrochloride. Work capacity increased after this. Muscle weakness, therefore, was not due to direct action of ergotamine tartrate. The author postulates that some predisposing factor of migraine must potentiate the slight effect of ergotamine tartrate on striated muscle. The work capacity was slightly increased by a placebo injection.

*Systemic Allergic Reaction Induced by Yellow Fever Vaccine.* Swartz, Harry: Jour. Lab. & Clin. Med., 28:1663, 1943.

Case report of anaphylactic type response in egg-chicken-sensitive patient to a single immunization injection of yellow fever vaccine. Vaccine proven to be instigating agent by P-K testing. Evidence offered to substantiate statement that reagenic fraction of yellow fever vaccine is related to both egg white and chicken meat, but resembling former more closely. Egg and chicken sensitivity by history or skin test is an indication to give yellow fever vaccine carefully.

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(Continued from Page 286)

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# News Items

## ANNUAL MEETING OF BOARD OF REGENTS

At the annual meeting of the Board of Regents of the American College of Allergists, held at Cleveland, June 2 and 3, the following Associate Fellows were elevated to Active Fellowship in the organization:

- Dr. Leon Bentolela, Buenos Aires, Argentina
- Dr. James T. Burns, Washington, D. C.
- Dr. C. H. Glover, Memphis, Tennessee
- Dr. Edley Jones, Vicksburg, Mississippi
- Dr. Stephen T. Manong, Niagara Falls, New York
- Dr. Benjamin Zolov, Portland, Maine

Membership in the College, reported at this meeting, was: Active Fellows, 390; Associate Fellows, 55; Honorary Fellows, 15; Corresponding Fellows, 3; Total, 463.

Those nominated to the various offices in the College, whose names were listed on the mail ballot sent to all Active Fellows, received a majority vote. Their terms of office extend from July 1, 1945, to July 1, 1946. The officers elected are:

- President, Dr. Harry L. Rogers, Philadelphia, Pennsylvania
- President-Elect, Dr. Leon Unger, Chicago, Illinois
- First Vice President, Dr. Hal M. Davison, Atlanta, Georgia
- Second Vice President, Dr. Michael Zeller, Chicago, Illinois
- Secretary-Treasurer, Dr. Fred W. Wittich, Minneapolis, Minnesota

The Regents elected to three-year terms, extending from July 1, 1945, to July 1, 1948, are:

- Dr. Hal M. Davison, Atlanta, Georgia
- Dr. Merle W. Moore, Portland, Oregon
- Dr. Homer E. Prince, Houston, Texas
- Dr. George E. Rockwell, Milford, Ohio

The Regents serving on the Board July 1, 1945 to July 1, 1946, are:

- Dr. Ethan Allan Brown, Boston, Massachusetts (1946)
- Dr. Hal M. Davison, Atlanta, Georgia (1948)
- Dr. Merle W. Moore, Portland, Oregon (1948)
- Dr. Homer E. Prince, Houston, Texas (1948)
- Dr. George E. Rockwell, Milford, Ohio (1948)
- Dr. Harry L. Rogers, Philadelphia, Pennsylvania (1947)
- Dr. J. Warrick Thomas, Richmond, Virginia (1946)
- Dr. Leon Unger, Chicago, Illinois (1947)
- Dr. Orval R. Withers, Kansas City, Missouri (1946)
- Dr. Fred W. Wittich, Minneapolis, Minnesota (1946)

It was voted to conduct an intensive instructional course in allergy next November 5 to 10, inclusive, at Northwestern University, Chicago, Illinois, with clinical facilities at Wesley Memorial Hospital. The schedule of subjects was arranged, and the speakers named.

The "Committee on Graduate and Undergraduate Education in Allergy" will be known as the "Educational Committee" of the College.

Dr. Louis S. Robins, Chicago, an Active Fellow in the College, was elected to the Editorial Staff of the ANNALS OF ALLERGY.

## NEWS ITEMS

It was decided that the Progress in Allergy notes and Annual Reviews of the Literature, appearing in the ANNALS, be bound each year.

The Spanish supplement, which is published under the auspices of the College and which contains abstracts in Spanish of the scientific articles appearing in the ANNALS, will carry Spanish advertising and will also be enlarged to include Spanish translations of the Progress in Allergy notes and the Reviews of the Literature.

It was voted to publish a roster of College Fellows in January, 1946.

Dr. George R. Rockwell, Chairman of the Standardization Committee, reported on the progress which this Committee has made so far. Editorials will appear in future issues of the ANNALS concerning the plans for the work to be done and the accomplishments attained by this Committee.

The subject of certification of allergists was discussed, and it was decided that this matter be tabled until the next annual meeting of the Board of Regents.

It was planned to hold the next annual meeting of the College in 1946, just prior to that of the American Medical Association, in the same manner as the 1944 meeting of the College was conducted.

It was voted to establish an Honor Section of the College. This will be known as an Advisory Council to the Board of Regents. Membership in this Section will signify the highest distinction a Fellow can attain in the College. Eligibility to membership in the Honor Section will require 20 points which will be apportioned as follows: Officers will receive one point for each year in office; instructors, two points for each course presented; papers published in the ANNALS will be rated according to their content and length.

The functions of the New and Unused Therapeutics Committee, of which Dr. Ethan Allan Brown is Chairman and of which Drs. L. O. Dutton, Philip M. Gottlieb, George E. Rockwell, Frank A. Simon and Erich Urbach are members, will be initiated. It was decided that a page headed "New and Unused Drugs" be included in the ANNALS in which articles will be published which will be signed by the member of the Committee making the report or by the Chairman of the Committee. The literature concerning important drugs will be reviewed and given a trial, when feasible. Members will be asked to submit questions concerning drugs. Certain preparations about which there has been controversy will be investigated first.

The Questions and Answers department of the ANNALS will be revived. Members are urged to submit questions which will be referred to the best known authorities for reply.

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## THE INTERNATIONAL ASSOCIATION OF ALLERGISTS

After careful planning and study by representative officers of the most important existing national allergy societies, it has been mutually agreed to organize an International Association of Allergists. The time is considered opportune, with the cessation of global conflict and the accelerated universal interest of medical men in applying allergy to their various specialties, for an association which would encourage and promote international assemblies for the purpose of disseminating information relating to allergy throughout the world. Pan American and Pan European Sections will be affiliations of the Association.

Plans are in progress for holding the first International Congress in Paris in 1948 when universal standards of terminology and classification of allergies will be adopted.

Preliminary to this program, it is proposed that the same subjects will be the theme of the first Pan American Congress to be held under the auspices of the College at its next annual meeting.

The College is very fortunate in having some of its officers invited to participate in the organization of this association by the officers of the outstanding al-

## NEWS ITEMS

lergy societies of other nations. The Board of Regents has officially accepted the proposals offered by the International Association. Standards for eligibility to membership and all other important functions are now being formulated and incorporated into the By-Laws.

### MEMBERSHIP

At the June meeting of the Board of Regents of the College, the following members were elevated to Active Fellowship in the organization:

Dr. C. H. Glover, Memphis, Tennessee  
Dr. Edley H. Jones, Vicksburg, Mississippi  
Dr. Stephen T. Manong, Niagara Falls, New York  
Dr. Benjamin Zolov, Portland, Maine  
Dr. Leon Bentolila, Buenos Aires, Argentina

Those elected to Active Fellowship during June and July, 1945, are:

Dr. William Roland Crowe, Atlanta, Georgia  
Dr. Royal H. Finney, Pueblo, Colorado  
Captan Kenneth J. Weiler, Tampa, Florida

Associate Fellows elected to membership during June and July, 1945, are:

Major Irwin Alters, Overseas  
Dr. William H. Blank, Birmingham, Alabama  
Lt. B. B. Burrill, Bainbridge, Maryland  
Dr. Robert E. Jameson, Davenport, Iowa  
Dr. Howard J. Lee, Hamilton, Ontario, Canada  
Captain Benjamin Lieberman, Oakland, California  
Dr. Emanuel C. Liss, South Bend, Indiana  
Dr. Frank C. MacCardell, Providence, Rhode Island  
Dr. Lewis B. McCullough, Mansfield, Ohio  
Dr. Morris Scherago, Lexington, Kentucky

### ANNOUNCEMENT

#### **The Manual of Allergy Laboratory and Diagnostic Procedures**

This practical, new, revised Manual, compiled by members of the College, is ready for mailing. The supply of the first mimeographed edition, issued at the St. Louis instructional course last fall, having soon become exhausted, a second, enlarged, printed, loose-leaf edition (8½ x 11), permitting supplemental or revised procedures, has been published. It is bound in a standard ring book of exceptional, durable quality. The Manual includes detailed methods of making allergenic extracts of all kinds and their standardization. The table of contents is a complete guide to the material included.

Preseasonal, perennial and coseasonal treatment is fully described. All the various methods of testing for allergies are given. An authoritative zonal map, showing the prevalence and distribution of pollens, is illustrated. The indications and detailed directions for the administration of histamine are presented. Immunologic tests are described.

The sales price for the Manual is \$3.75, based upon the cost of production only. Any surplus, due to unpredicted sales, will be applied to the College Research Fund.

AMERICAN COLLEGE OF ALLERGISTS

401 La Salle Medical Building  
Minneapolis 2, Minnesota

## NEWS ITEMS

The Board of Regents is pleased to announce the election to Honorary Fellowship in the College of Dr. Jiminez-Dias of Madrid, Spain, Dr. Pasteur Vallery-Radot of Paris, France, and Dr. Abelardo Saenz of Montevideo, Uruguay, for their outstanding and meritorious contributions in the field of allergy. The College's efforts to foster and encourage a friendly international co-operation of specialists interested in allergy has been rewarded by the tentative mutual plans already made for the holding of a Pan American Congress of Allergy under the auspices of the College at its next annual meeting to be held next June with the American Medical Association.

Dr. Edward A. Dickson, an Active Fellow of the College, has announced the opening of his office for the diagnosis and treatment of allergy at 19 Garfield Place, Doctors Building, Cincinnati 2, Ohio.

**WANTED: RESIDENTS OR FELLOWS IN ALLERGY.**—Facilities for clinical study and research available. Periods of training from 6 months to 2 years with compensation. Vaughan Memorial Clinic, 201 West Franklin Street, Richmond 20, Virginia.

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# ANNALS *of* ALLERGY

*Published by the  
American College of Allergists*

Volume 3

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Number 5

## THE CONJUNCTIVAL TEST AS A GUIDE TO CLINICAL IMMUNITY IN HAY FEVER

MARY HEWITT LOVELESS, M.D.  
New York, New York

THERE is at present no criterion by which the allergist assesses, in advance of the season of pollination, the adequacy of his specific therapy against hay fever. If such a yardstick were available, injections could be adjusted to the individual's needs instead of being given on an empirical basis.

Previous studies have suggested that the clinical improvement which is noted in pollen-sensitive patients after a series of injections may be related, at least in part, to the development of thermostable antibodies in their blood<sup>3</sup> and allergic tissues.<sup>2</sup> It appears that these bodies raise the local tolerance by binding the pollen antigen. If this theory is correct, then determining the state of susceptibility of the eye just prior to the season should give a clue to the probable behavior of the patient during the time of pollination. It was the purpose of the present investigation to test this possibility.

### MATERIAL AND METHODS

*Patients.*—Ninety-five individuals were observed during 1943 and 1944, forty-four of them being studied during the two years. Comparison was made between the threshold of conjunctival reaction found at the onset of the season and the degree of clinical refractoriness subsequently noted while ragweed was in bloom. There were 139 such sets of data available for the group. All members gave typical histories of autumnal hay fever and showed the characteristic responses when tested by intracutaneous, conjunctival, nasal and passive sensitization techniques. Just prior to the conjunctival tests, a course of treatment with ragweed

From The New York Hospital and the Department of Medicine, Cornell University Medical College, New York, N. Y.

Presented in part before the first annual meeting of the American College of Allergists, Chicago, June 10 and 11, 1944.



extract had been given each patient. In thirty instances, this was the subject's first course. For all others, it was a booster course which consisted in many cases of a total of 10,000 protein nitrogen units administered in seven injections.

*Antigen*.—Ether-defatted pollen was extracted for twenty-four hours in Coca's alkaline saline solution. The solutions were standardized on the basis of their phosphotungstic-acid-precipitable nitrogen. In order to minimize the aging of the antigen, one large batch was frozen and dried for all the 1943 experiments so that samples could be freshly dissolved every few weeks; and new extracts were prepared every other week during the 1944 studies.

*Conjunctival Tests*.—The patient was seated facing the source of daylight. The tester stood about four feet in front of the subject in order to judge the color of the conjunctivae and especially of the caruncles. One eye was used for the test, the other serving as control. The test dose was one fully-rounded drop, hanging from a 26-gauge hypodermic needle (Vim). The drop was brought upward in front of the cheek with the needlepoint directed away from the orbit. The drop was gently touched onto the everted lower lid at the moment the patient was asked to look upward at some object (to prevent blinking).

The initial strengths used were so dilute as to cause no reaction. Each five minutes more concentrated antigen was introduced until the first signs of reddening of the caruncle appeared. This was recorded as the threshold dose. Stronger solutions were then used until decided irritation and itching occurred, in confirmation of the threshold response. The sac was then flooded with physiological saline solution, and a few drops of epinephrin 1:1000 finally instilled. Tests, performed before a course of therapy, had been initiated with extract containing 1 P.N. unit per c.c. and carried on with 10-unit, 25, 50, 100, 150, 200, 300-unit solution or stronger until the first reaction point had been located and passed. After the course, the test was repeated in the other eye, commencing with the strength just below that which had provoked the threshold response formerly.

As a preliminary investigation into the reliability of the test, thirty-two individuals of the group were subjected to a second test which was carried out in the same eye two weeks later by a different tester. It was felt that any influence of a preceding test would be detected by this procedure.

*Estimating Clinical Immunity*.—The patient was asked to judge the extent of his improvement by comparing his current season with those previous to treatment. As a check on this somewhat unreliable yardstick of clinical progress, each was required to keep a daily record of symptoms in terms of hours and of severity. Many of the members of the group had kept such records for us for several years.

# CONJUNCTIVAL TEST—LOVELESS

TABLE I. THRESHOLD VALUE OBTAINED WHEN CONJUNCTIVAL TEST WAS REPEATED BY A SECOND OPERATOR AFTER AN INTERVAL OF TWO WEEKS

Case	Threshold Reaction of Conjunctiva			
	Initial Test (P.N. units)	Retest	Second Tester	Level of Second Threshold
1	10	1	ML	lower
2	5	5	ML	same
3	10	10	ML	same
4	10	25	ML	higher
5	25	15	ML	lower
6	25	5	HS	lower
7	25	10	ML	lower
8	25	15	HS	lower
9	25	25	ML	same
10	25	25	ML	same
11	25	25	HS	same
12	25	25	ML	same
13	25	100	ML	higher
14	25	25	ML	same
15	50	10	ML	lower
16	50	25	HS	lower
17	50	50	ML	same
18	50	10	HS	lower
19	50	50	HS	same
20	75	100	HS	higher
21	75	200	HS	higher
22	75	50	HS	lower
23	75	200	HS	higher
24	100	75	ML	lower
25	100	35	HS	lower
26	100	150	HS	higher
27	100	400	HS	higher
28	150	200	HS	higher
29	200	100	HS	lower
30	200	100	ML	lower
31	275	275	HS	same
32	350	275	ML	lower

## POLLEN COUNTS

*Pollen Count*—The concentration of ragweed pollen grains in the air amounted to 1,356 per cubic yard when the daily figures for August and September of 1943 were totaled. The comparable count for 1944 was 1,702 whereas the average for fifteen years amounted to 1,756. These data are based on slides which had been set out in the New York Meteorological Observatory of Central Park by Mr. David Morris, of the U. S. Weather Bureau, and which were analyzed by Mr. O. C. Durham.

Table I shows the conjunctival thresholds determined independently by two different operators when patients were retested after a two weeks' interval. Half the group were given the initial test by one worker, while the remaining sixteen cases were first examined by the other. It will be seen that the duplicate studies brought comparable results in most instances, despite the fact that different extracts were used and that the same eye was tested on the two occasions. Table II indicates that the result of

# CONJUNCTIVAL TEST—LOVELESS

TABLE II. LEVEL OF THRESHOLD REACTION DURING SECOND TEST

Tester	Higher than in 1st Test (No. cases)	Lower than in 1st Test (No. cases)	Same as in 1st Test (No. cases)
H.S.	6	7	3
M.L.	2	7	7
Total	8	14	10

TABLE III. RELATION BETWEEN THRESHOLD OF CONJUNCTIVAL RESPONSE AND CLINICAL RESULT  
(139 Courses given in 1943 and 1944)

Threshold of Reaction in Conjunctiva after course (P.N. units)	CLINICAL RESULT			
	Excellent (90-100% relief) No. of Cases	Good (75-85%) No. of Cases	Fair (50-70%) No. of Cases	Poor (Less than 50%) No. of Cases
15		1		
25	2	2	3	1
35			1	1
50	2	5	3	1
75	2			
100	7	10	5	3
150	7	4	3	1
200	5	6	6	2
300	12	9		2
350	3	2		
400	4	5		1
450	2			
500	1	3		
600	1	1		
800	1			
1000	3	2	1	1
2500	1			
4000		1		
Total	53	51	22	13

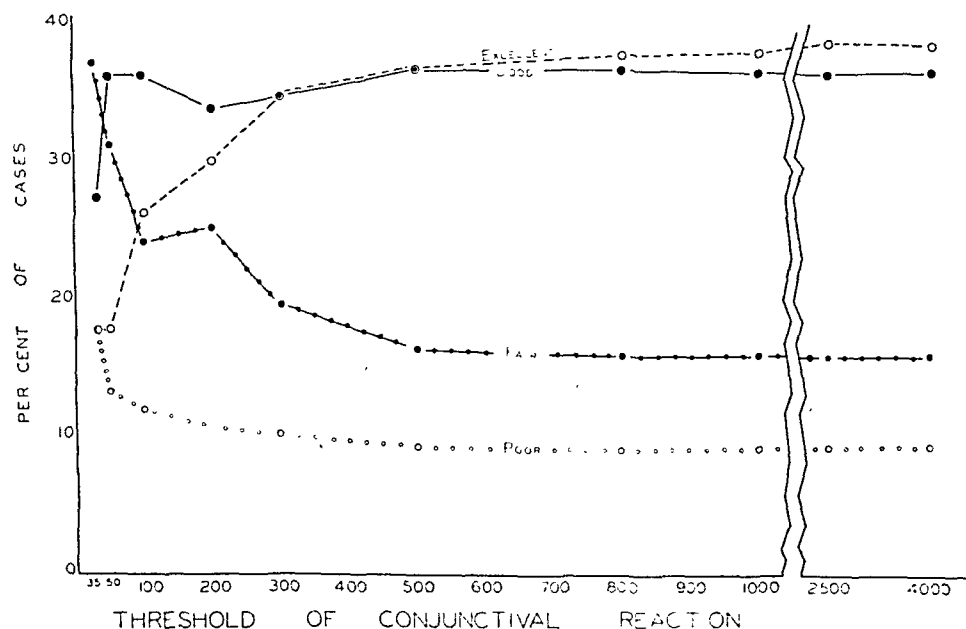
the second test was identical with that of the first in ten cases, and was somewhat lower in fourteen others. The latter figure was partially counterbalanced by eight instances in which the second result was greater than the first. One can conclude from this experiment that the conjunctival test does not vary significantly with (a) two testers who have been trained to read in the same manner, (b) two successive extracts standardized similarly, or (c) a prior test performed on the same eye several weeks beforehand. It seemed possible that a test might lead to local immunity and thus falsely color the result of a subsequent one. This possibility can presumably be discarded for the technique employed, since 75 per cent of the group showed identical or slightly lower thresholds to retest.

Following their 139 courses of treatment in 1943 and 1944, our ninety-five patients were found to have conjunctival thresholds of reaction which ranged from 15 to 4,000 units, as indicated in Table III. The number

# CONJUNCTIVAL TEST—LOVELESS

TABLE IV. PROPORTION OF CASES WITH SATISFACTORY CLINICAL IMPROVEMENT OCCURRING AT VARIOUS CONJUNCTIVAL THRESHOLDS

Conjunctival threshold (P.N. units)	Number of Cases with Satisfactory Result	Total number of Cases with this Threshold	Proportion of Cases with Satisfactory Result
35 or less	5	11	49%
50	7	11	63%
75, 100	19	27	70%
150, 200	22	34	65%
300	21	23	91%
350, 400, 450, 500	20	21	95%
600 to 4000	10	12	83%
Total	104	139	75%



of subjects reporting excellent, good, fair and poor clinical results in connection with these various thresholds is listed. It will be seen that most of the group could tolerate between 50-unit and 400-unit solution before showing visible irritation in their eyes, the greatest concentration of cases being in the vicinity of 100 to 300 units. Those thirty-five cases experiencing fair and poor improvement were found to have seasonal thresholds of less than 350 in all but three instances. The ratio of unsatisfactory to satisfactory result was one to each 2.3 cases for thresholds below 350; whereas, among patients with higher conjunctival resistance, the ratio was 1 to 10.

Table IV shows that the proportion of satisfactory to unsatisfactory clinical results increased from the low thresholds to the higher ones. In-

# CONJUNCTIVAL TEST—LOVELESS

TABLE V. COMPARISON BETWEEN CONJUNCTIVAL THRESHOLD AND PERCENTAGE OF CASES WITH EXCELLENT OR GOOD CLINICAL RESULT

Threshold of Conjunctival Reaction	Number of Cases with Excellent or Good Result	Total number of Cases with this Threshold	Per Cent with Excellent or Good Result
35 or less	5	11	45.4
50 or less	12	22	54.5
75 or less	14	24	58.0
100 or less	34	49	62.6
150 or less	42	64	65.6
200 or less	53	83	63.8
300 or less	74	106	69.8
350 or less	79	111	71.1
400 or less	88	121	72.7
500 or less	94	127	74.0
600 or less	96	129	74.4
800 or less	97	130	74.6
1000 or less	102	137	74.4
2500 or less	103	128	74.6
4000 or less	103	139	74.1

dividuals whose eyes reacted to extract as dilute as 35 units per c.c. reported excellent or good relief in less than half of the instances. Among those whose thresholds lay in the region of 300 to 500, satisfactory results were obtained by over 90 per cent.

This tendency for clinical tolerance to rise with conjunctival tolerance can also be seen in the graph. Among the cases with thresholds of 35 or less, the incidence of excellent clinical response was two per eleven subjects, or 18 per cent. This same ratio applied for the 22 patients whose preseasonal thresholds were located at or below 50, 18 per cent of them experiencing almost complete loss of their hay fever. From this point on the graph, there is a sharp and steady increase in the proportion of cases with highly satisfactory clinical progress until at 300, 35 per cent of the accumulated patients from this and lower levels reported excellent control of their seasonal complaints. There was a slight improvement in the curve with still higher thresholds, but the number of cases added at these levels was small and the figures, therefore, are of less statistical significance.

Except for a preliminary peak in the region of 50 and 100, the curve for patients reporting a loss of three-quarters to 85 per cent of symptoms is similar to that of the above group. In contrast to these, the curves for patients with fair and with poor clinical results show a tendency to drop to lower levels as the related conjunctival threshold values rise.

If the curves for patients with excellent and good clinical results were combined, it would be found that satisfactory control of symptoms occurred in 45 per cent of cases with thresholds of 35 or less, in 63 per cent of those with thresholds of 100 or less, in 70 per cent of those with thresholds of 300 or less and in approximately 75 per cent of those whose oph-

## CONJUNCTIVAL TEST—LOVELESS

thalmic responses were at 500 or below (Table V). Until this level was reached, therefore, the incidence of good results tended to be greater as the thresholds were higher.

### DISCUSSION

In seeking an objective index to clinical immunity in hay fever, the author first investigated the serum antibodies. Although these thermostable, pollen-binding bodies are present in normal and in allergic individuals alike following their parenteral treatment with pollen extract and although their concentration appeared to vary with the clinical refractoriness of the patient<sup>3</sup>, there are practical disadvantages to using the antibody titer as a guide to treatment. For one thing, the technique of passive sensitization is specialized, exacting and time-consuming. For another, the result obtained varies definitely with the choice of a normal test-subject. The number of comparisons must therefore be restricted. This makes it very difficult to determine *absolute* levels of humoral immunity and precludes the drawing of comparisons among sizable groups of individuals for the establishment of standards. The second objection may be overcome by the future development of the precipitin method of Hampton, Johnson, Alexander and Wilson.<sup>1</sup>

The conjunctival test does not carry these two disadvantages of the passive transfer technique. It is simple to perform, requiring no special training for the physician and no special equipment. It takes but a short time to complete. It is painless and safe providing simple precautions are taken. Since it is performed upon the patient himself and on one of the natural "shock" organs of hay fever, it should yield more accurate information than a test carried out in the skin of some test-subject. Furthermore, in assessing the pollen-binding power of a "post-treatment" serum, only one factor (namely, the thermostable antibody) is being studied whereas other important ones are disregarded. These other agents are the patient's reagins and other unknown "host" factors which undoubtedly play a role in the ultimate behavior of the allergic subject. Another point worth considering is the probability that the immune bodies which are circulating in the bloodstream play no immediate part in allergic manifestations. They are too remote from the portals of entry of the pollen in the eye and respiratory tract. The pollen antigen will have been combined with either the thermostable or the reaginic bodies in the tissues before reaching the circulation. Although it appears that a balance exists between the concentration of antibodies in the tissues and those in the bloodstream<sup>3</sup>, this equilibrium might theoretically be disturbed at times and the antibody concentration of the serum might then be an unreliable index to the tissue immunity. It would seem wiser to test the tissue itself.

The tissue usually tested by allergists is the skin. Less constant and less valuable information has been obtained in the writer's hands with

skin-testing (even of the most controlled, threshold type) than with the conjunctival test<sup>4</sup>, as will be shown in an early report. The nasal test has been found to yield more trustworthy data but has been associated with unpleasant after-effects.

The present study has indicated that the threshold test of the conjunctiva offers considerable promise as a guide to the state of immunity in pollinosis. Additional observations are being made during the current hay fever season. Although some members of our group experienced excellent results with relatively low thresholds of conjunctival reaction, the incidence of satisfactory clinical response appeared to be greater among patients with thresholds in the region of 300 to 500. Until more data are available, it will be our practice to treat the newly acquired patient with booster doses which will, if possible, bring his conjunctival threshold to these levels. Once he has been watched through a successful season, the related ophthalmic threshold noted during that season can serve as the goal for future therapy. By studying the eye at intervals during these future courses, it will be possible to ascertain what the minimal requirements in dosage are. Individualizing therapy in this way should tend to bring each patient optimal results in minimal time, avoiding both under- and overtreatment.

#### CONCLUSIONS

1. A modification of the conjunctival test, designed to reveal the threshold of reaction toward pollen extract, is described.
2. Preliminary studies indicated that the test varies unimportantly with the operator, with two extracts of the same pollen, and with an interval of a few weeks. A preceding test did not influence appreciably the threshold value found in a second test two weeks later.
3. Although some patients experienced successful seasons with conjunctival thresholds which were relatively low, in general, the clinical results were better as the thresholds were higher. Among ninety-five cases observed for one or two ragweed seasons, 95 per cent of those with thresholds of 350 to 500 reported good or excellent clinical results, whereas only 49 per cent of those with thresholds of 35 or less showed satisfactory clinical control of their hay fever. It would seem indicated to give newly acquired patients "booster" courses adequate to raise the thresholds to at least 300, if possible.
4. The conjunctival threshold test gives promise of serving as a guide to the amount of specific treatment required by the hay fever case. Average figures for the group may be useful as crude indices to the needs of the newly acquired patient, until such time as his own "protective" threshold can be established by the test of one or more seasons.

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The writer wishes to express appreciation to Miss Helen Schneemann for technical assistance during these studies.

## MOLD ALLERGY

### II. Clinical Analysis

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CONSIDERABLE controversy has existed regarding the incidence of mold allergy since van Leeuwen<sup>12,13</sup> first called attention to the important role that molds play in precipitating allergic symptoms. At first only sporadic reports of mold allergy appeared in the literature, but with the advent of Feinberg's<sup>4</sup> work, more extensive surveys began to appear. Most of these reports emanated from the midwest where mold allergy was more prevalent, or was recognized to a greater extent than in other parts of the country. This was at first attributed to the peculiar flora of the locality and the high concentrations of atmospheric mold spores, but it shortly became evident that mold allergy existed throughout the United States. The incidence given in each report, however, varied greatly, depending largely upon the locality in which the survey was made. The criteria for establishing a diagnosis of mold allergy likewise varied, making it difficult to correlate or compare the results.

Lamson and Rogers<sup>7</sup> report an incidence of 12.2 per cent positive skin tests in a series of 1,259 patients, but make no mention of the incidence of clinical sensitivity. Schonwald<sup>11</sup> reports 57 per cent positive skin reactions to molds in a series of 150 allergic patients, with 76.7 per cent improvement after adequate mold therapy. Pratt<sup>9</sup> reported over 25 per cent positive skin reactions in a group of 177 atopic children. Jimenez et al.<sup>6</sup> found seventeen mold-sensitive patients in a group of 292 allergic patients, an incidence of 5.8 per cent. Vander Veer<sup>14</sup> reports thirteen positive skin tests in a series of eighty allergic patients tested, an incidence of 16.25 per cent. Chobot et al.<sup>3</sup> reported an incidence of 26.5 per cent positive skin tests to *Alternaria* among an unselected group of 244 allergy patients. No attempt was made to determine the incidence of clinical sensitivity in this group although twelve out of twenty-eight selected patients were constitutionally sensitive. Pennington<sup>8</sup>, in studying a group of 526 patients, found sixty-seven who presented a suggestive history of mold allergy. Provocative tests were done on sixty-one of these patients and only twenty-two were found positive. Thus twenty-two of a group of 526 patients (4.2 per cent) exhibited definite mold allergy.

The percentage of positive skin reactions in the above reports varies from 5.8 to 57, while clinical sensitivity varies from 4.2 to 42 per cent. These divergent results seemed too great to be reliable. They suggested dissimilar methods of investigation and lack of uniformity in the preparation of extracts and in the criteria for determining clinical sensitivity. The present study was undertaken in an effort to clarify this situation

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and also to search for the offending factors in patients with seasonal hay fever and asthma that were not attributable to any of the known airborne allergens in this locality.

## PROCEDURE

Thirteen known mold cultures were selected either because of reports of clinical sensitivity to them in the literature, or because of the relative frequency with which they were found on our exposed slides and plates. Each of these was subcultured in a 500 c.c. Erlenmeyer flask containing between 50 and 75 c.c. of a broth made up as follows:<sup>5</sup>

Distilled water	5,000 c.c.	Sodium chloride	25 Gm.
Peptone (Armour)	50 Gm.	Meat Extract (Armour)	25 Gm.
Autoclave. Filter. Add maltose 100 Gm. Autoclave in large flasks.			

Maximum growth was attained in three weeks. The mold pellicle was then removed and placed in a Bard-Parker sterilizing jar over 40 per cent formalin for twenty-four to forty-eight hours. This killed all the molds and permitted us to work with extracts of dead organisms. The material was air-dried and ground into a fine powder from which was prepared a 3 per cent extract of mold powder in Coca's solution.\* Nitrogen determinations were done on all extracts and for testing purposes they were diluted so as to contain .1 mg. Total N per cubic centimeter.

All patients attending the allergy clinic were tested with these materials. This assured us of a heterogenous group of thoroughly studied allergic patients. All patients exhibiting positive skin reactions to the mold extracts were then tested by the nasal route with the corresponding mold powder. If it could be proved that the powders used were non-irritating, then any resulting reaction could be attributed to specific sensitivity. Blood was obtained from each reactor and passive transfer tests done to demonstrate the presence or absence of sensitizing antibodies. Patient's symptoms were then correlated with the atmospheric mold concentration. Other things being equal, a direct relationship should have existed between the severity of symptoms due to mold allergy and the atmospheric mold concentration.

## RESULTS

Four hundred six allergic patients were thus studied. One hundred sixty-nine displayed positive skin reactions to one or more mold extracts, an incidence of 41 per cent. Table I shows the frequency with which each mold reacted, and the degree of reactivity.

*Na Cl	0.5	per cent
Na HCO <sub>3</sub>	0.275	per cent
Phenol	0.4	per cent

It will be noted that the majority of the skin reactions were only slightly positive (+). As will be shown later, a large proportion of these reactions were nonspecific and therefore of no clinical significance. When of greater intensity, they were just as pronounced as those seen in cases

TABLE I. FREQUENCY AND INTENSITY OF SKIN REACTIONS TO MOLD EXTRACTS

Degree of Reaction	+	++	+++
<i>Alternaria</i>	21	12	8
<i>Aspergillus flavus</i>	15	1	0
<i>Aspergillus fumigatus</i>	11	0	0
<i>Cephalosporium</i>	38	6	0
<i>Fusarium</i>	20	0	0
<i>Helminthosporium</i>	22	4	0
<i>Hormodendrum</i>	19	3	3
<i>Monilia sitophila</i>	25	6	2
<i>Mucor</i>	35	3	2
<i>Penicillium digitalis</i>	21	4	0
<i>Rhizopus</i>	17	3	0
<i>Torula</i>	15	3	0
<i>Trichophyton</i>	22	1	0

of pollinosis. The most frequent skin reactors were *Alternaria*, *Monilia*, *Hormodendrum*, *Mucor*, *Cephalosporium*, *Helminthosporium*, *Penicillium*, *Rhizopus*, *Torula*, *Trichophyton* and *Aspergillus flavus*, being named in the order of importance.

Each subject yielding positive skin reactions was further tested by the nasal route.<sup>1</sup> The mold powder used in each case corresponded to the extract producing the positive skin reaction. A positive reaction consisted in the precipitation of hay fever or asthma-like symptoms similar to those complained of by the patient. Such a reaction was regarded as specific and indicated the presence of clinical sensitivity unless it occurred in patients with a hyperesthetic rhinitis. The inhalation of any particulate substance in the latter type is followed by a rhinitis of non-specific character. Twelve patients showed positive reactions to the inhalation of various mold powders. Table II depicts the number and the various types of patients tested, the number of positive skin reactions and the percentage of clinically sensitive patients in each group.

Thus of 406 patients studied, 169 (41 per cent) gave positive skin reactions, while only twelve (3 per cent) displayed clinical sensitivity. It will be noted that all cases of mold allergy occurred in patients with seasonal symptoms, accounting for twelve of 133 cases, an incidence of 9 per cent.

An effort was then made to determine the existence of any special clinical features that might aid in its clinical recognition. A review of the histories of these twelve patients revealed the fact that ten presented symptoms of asthma while the remaining two complained only of seasonal rhinitis. In the group as a whole, itching of the eyes was a minor com-

# MOLD ALLERGY—BLUMSTEIN

TABLE II. DISTRIBUTION OF MOLD SENSITIVITY AMONG VARIOUS TYPES OF CLINICAL ALLERGY

	No. of Patients	Positive Skin Reactors	Clinical Sensitivity
Seasonal hay fever	121	66	2
Perennial hay fever	80	31	0
Seasonal asthma	12	11	10
Perennial asthma	158	51	0
Urticaria, eczema, migraine, contact dermatitis, vernal conjunctivitis	35	10	0
	406	169 (41%)	12 (3%)

plaint, a differential point that might aid in distinguishing it from pollen hay fever where this is a rather constant and annoying symptom. Another aid in the differentiation of mold allergy from pollinosis was found in the duration of their symptoms. The patients with mold allergy had active clinical symptoms without remission during the period of sporulation, that is, from May to November.<sup>2</sup> A symptom period of this type could not be explained by the pollination of any group of plants, for there invariably is a remission of symptoms between the grass and weed seasons (late July and early August). Many of the patients in this group had previously been treated unsuccessfully with various mixtures of pollen extracts.

Multiple clinical mold sensitivity existed in seven of the twelve cases. The offending molds in their order of importance are *Alternaria* (10), *Hormodendrum* (5), *Monilia* (3), *Helminthosporium* (2), and *Mucor* (1). Three of the twelve patients gave specific positive nasal tests with each of the thirteen mold powders tested. Reactions of this type may have been due to some irritating substance derived from the culture material and therefore common to all the powdered extracts. Positive nasal reactions were obtained in these individuals by agitating petri dishes containing agar cultures of each of the molds in question. The spores were thus liberated without an admixture of culture material and disproved the above concept. A satisfactory explanation for this phenomenon is still lacking.

The frequency of an associated pollen factor in eight of the twelve patients serves to call attention to the multiple allergens that may act as contributing factors in seasonal allergies.

Passive transfer tests with the serum of ten of the twelve clinically sensitive patients yielded positive tests for the presence of sensitizing antibodies. These sensitizing antibodies were specific for each mold and the reaction to one mold extract could not be obliterated by neutralization or exhaustion by the previous addition of another.

## DISCUSSION

Mold allergy occurred in 3 per cent of 406 allergy patients in this series, or in 9 per cent of the seasonal cases. This should tend to place

the main emphasis on the pollens as the cause of seasonal allergies and reserve a secondary role for the less frequent mold factors. Mold allergy should be suspected in patients presenting seasonal variations in symptoms that are not attributable to the usual seasonal pollen factors.

The clinical symptomatology varies with the individual patient but differs sufficiently from cases of pollinosis to be of clinical value. Complaints referable to the eyes were minimal in most cases and could be elicited only with great difficulty. This differs from pollinosis where eye symptoms are prominent and quite annoying. Nasal symptoms, although present in each of the twelve patients, constituted the chief complaint in only two. The remaining ten suffered with seasonal asthma. The period of suffering in mold allergy does not correspond with the pollinating period of any pollen or group of pollens. Symptoms are most severe, as a rule, in July and August, when the pollen concentration in the air is lowest and the spore count highest. There is no period of remission in mold allergy such as occurs in pollen allergy between the grass and weed seasons. Thus, mold allergy may be suspected clinically in individuals presenting themselves with seasonal, unremitting symptoms, especially asthma, that do not correspond with the pollinating period of any group of pollens.

The skin tests in clinically sensitive patients were just as definite and specific as occurred with pollen in cases of hay fever. Mold extracts should not be used routinely for skin testing because of the low incidence of sensitivity in the allergy group as a whole. Its use is indicated in those cases of seasonal allergy that are not due to pollen, or those cases of pollinosis where a complicating mold allergy may co-exist and be responsible for poor therapeutic results. It is not necessary to test with all the molds used in this study. The extracts suggested for skin testing are those that have been found capable of producing clinical symptoms and include *Alternaria*, *Hormodendrum*, *Monilia*, *Helminthosporium*, *Cephalosporium* and *Mucor*.

As already indicated, the reason for such divergent percentages of clinically sensitive cases in the available reports depends upon two factors: first, the locality in which the survey was made, and secondly, the lack of uniform criteria for judging clinical sensitivity. Increases in the atmospheric pollen or mold concentration has never influenced the percentage of sensitive patients in a given locality and could not explain the variability in clinical sensitivity. A more likely explanation would seem to be the failure on the part of investigators to utilize a simple, objective test for the determination of clinical sensitivity. The nasal test fulfills these requirements and was the provocative test used in this study. A patient was said to be clinically sensitive when the history corresponded to the period of sporulation and when positive skin and nasal tests were obtained. Some patients previously classified as pollen allergics with negative skin and nasal tests were properly categorized as cases of mold al-

lergy. Considerable skepticism should be cast upon the etiologic diagnosis of seasonal syndromes with negative skin and clinical tests. The offending agent in each instance should reproduce the symptoms exhibited by the patient.

The results of treatment with the appropriate mold extracts yielded uniformly good results. The failures encountered were in the same ratio as occurred in cases of pollinosis. Constitutional reactions were far more frequent in this series of patients than in a similar group with pollen allergy. This could be due to the lack of standardization of the mold extracts. No standard method for the preparation of mold extracts has been agreed upon. Pratt<sup>10</sup> has shown that the spores contain the allergen in much greater concentration than do the mycelia. His method of brushing the spores off petri dishes with a camel's hair brush has been found wanting for the yield was extremely small despite the use of dozens of petri dishes. The broth method of culture used in this experiment yielded a predominate growth of mycelia. Extracts prepared by both of these methods were actively allergenic when tested on sensitive patients. In an effort to imitate pollen collection and to have a standard parent substance from which extracts could be prepared, attempts were made to collect the spores directly from the host on which it grew. This procedure was finally abandoned because of the negligible yield and the difficulties encountered in determining the type of spore at the site of collection.

Other problems encountered during the course of this investigation warrant discussion. One of them is the occurrence of seasonal asthma in a small group of patients that could not be explained by any known air-borne allergen. Their season began in early to mid July and subsided by mid September. Clinically they resembled cases of mold allergy because of the paucity of hay-fever-like symptoms and the preponderance of asthmatic symptoms. The etiology of this group of patients remains to be determined.

Another difficulty was the lack of a competent mycologist with sufficient time to aid in the identification of mold cultures. Many plates were undiagnosed because of this deficiency. Many spores found on exposed slides failed to grow on a variety of culture media. The nature, origin and importance of these spores might be determined if a full-time mycologist was assigned to the problem. Knowledge of this sort might also aid in establishing the etiology of many seasonal asthmas now classified as "of unknown origin."

#### SUMMARY

1. Forty-one per cent of 406 thoroughly studied allergic individuals in this series displayed positive skin reactions to one or more of the thirteen mold extracts used in this study.
2. Twelve clinically sensitive mold subjects were found in this group—3 per cent of the entire group or 9 per cent of the seasonal group.

3. All these patients presented histories of seasonal allergies corresponding to the period of greatest mold concentration in the air. Ten of the twelve patients suffered from asthma, while eight manifested some type of pollen sensitivity in addition to their mold sensitivity.

4. A provocative test, in this case the nasal test, was used as an adjuvant in determining clinical sensitivity.

5. The only molds of etiologic significance in this study were *Alternaria*, *Hormodendrum*, *Monilia*, *Helminthosporium*, *Cephalosporium*, and *Mucor*, named in their order of importance. It is suggested that extracts of above be used for skin testing in patients suspected of being mold-sensitive.

6. Mold allergy may serve partly to explain the origin of many seasonal cases of hay fever and asthma that were previously considered to be cases of pollinosis with negative skin and clinical tests.

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*The Experimental Use of Ethylene Disulfonate (Allergosil Brand) in the Prevention of Anaphylaxis in Guinea Pigs.* Fish, R. T., Small, W. S., and Foord, A. G.: *J. Allergy*, 15:14, 1944.

Powdered egg albumin was used for sensitizing eighty-nine guinea pigs in four experiments. Thirty-three pigs "protected" with an injection of ethylene disulfonate showed a mortality rate of 60.61 per cent subsequent to shock dose, thirty-one pigs "protected" with an injection of water showed a mortality rate of 67.74 per cent. 25 untreated pigs showed a mortality rate of 72.00 per cent. Mathematically, the observed differences are within limits of standard error and chance. Conclusion reached was that ethylene disulfonate did not produce a significant degree of protection against anaphylactic shock.

# THE ORGANIC STATE IN THE PROBLEM OF ALLERGY

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THE allergic reaction of the tissues is reaction to a stimulus differing from the normal only in its speed and its intensity. It is a purposeful reaction—a reaction against the unusual or foreign. It is a reaction that involves the vascular tissues—the endothelium—the vessel coats—and, in so doing, the common clinical expressions elicited reflect rapid shifts in capillary permeability—rapid change in the tone of smooth musculature.

If in our study of the allergic reaction we are wholly preoccupied with the specific allergen (the effector) and are only incidentally concerned with the state of the effected tissues we will be confronted with inexplicable situations and paradoxical phenomena. Yet that is precisely what does happen in allergy and is precisely what happened for many years in the field of bacteriology and immunology.

As in all biological phenomena we have proceeded on the assumption that the organic reactions are simple and that the cause is single. Henderson<sup>2</sup> pointed out:

"There are certain deficiencies of the medical sciences to which little attention has been devoted. These deficiencies depend upon the fact that living organisms are immensely complex and that the experimental sciences, by hook or by crook, analyze the concrete reality into relatively simple elements. But the complex reality is never describable by merely adding up these elements, for they exist in a state of equally complex interaction. \* \* \*

"When men reason deductively about the complex affairs of everyday life, they nearly always leave out something, or rather many things, both things they forget and things they don't know. More often than not their conclusions are therefore unsound. This is what Whitehead calls 'the fallacy of misplaced concreteness.'"

"The fallacy of misplaced concreteness is very common in the form of arguments involving 'other things being equal.' In general, it may be said that all arguments involving such notions as other things being equal, or *pari passu*, are probably fallacious.

"The medical sciences have suffered and continue to suffer from this fallacy. The rise of bacteriology and its influence upon medical thought and practice may be taken as an example. About the time of Pasteur's first discoveries, the thought of Claude Bernard and of other physiologists seem to indicate a movement toward the study of the interrelations between many things and a recognition of this kind of study, synthetic physiology, as one of the foundations of the medical sciences and as the source of an indispensable point of view in all kinds of medical work. The discovery of specific pathogenic microorganisms to have led back to an oversimplification of thought about the origin and nature of disease. For some time at least, the tendency was to think of diseases as entities hardly less definite than atoms of oxygen or molecules or hemoglobin. Let us recall the fact that even hemoglobin *in situ* is not a single definite thing. The disposition was even more marked to think of the specific organism as the cause—the sole cause—of a specific disease, and later to think of the specific antitoxin as the specific cure of that dis-

ease. Similarly simple views of nutrition have prevailed. There was the epoch of calories; we now live in the epoch of vitamins. Hormones also are now having their day, and excess or deficiency of specific hormones, like excess or deficiency of particular vitamins, is often thought of as the cause of a specific disease."

So, too in allergy!

In the field of allergy, we tacitly assume that the subject's reaction to the allergen should be alike from day to day. Actually the organic state of the subject is never the same from day to day. But if reactivity varies, the reaction to an allergen will vary. It is this problem that will be discussed in the papers that follow.

The individual cell of the body exists in a state of unstable equilibrium—pendulating between two poles—activity and rest. We speak of this as the normal biotonus. Deviation from the normal biotonus in the direction of increased catabolism ("stimulation," increased oxidation, et cetera) may lead to fatigue and to death. Deviation in the opposite direction leads through inhibition (sleep) to a state of arrest that may persist for long periods of time but which usually ends in erosion. In the human, an integrated community of some eighteen or twenty billion cells, large numbers of individual cells can and do proceed through fatigue and to death without clinical reflection. The labile biotonus of the whole organism is maintained by the interplay of many individual checks and balances—for instance, the acid base balance, the water balance, the endocrine balance, the temperature balance, the lipoid balance, the calcium potassium balance, the ferment-antiferment balance—to mention but some of them.

Every energy impact upon the body must be equilibrated and the energy effectors are legion. The most common are changes in the immediate environment in which we exist—changes in light, in the air (temperature, humidity, electrical potential, et cetera), the cumulative effect of season, the character of food, work and exercise, the social milieu, the contact with the world of micro-organisms and allergens and toxins.

For the allergist the rôle of season is of great importance. Not only because of the seasonal tide of exposure to the botanical allergins (that we will ignore for the time being); *because the organic state of the patient is greatly modified with season!* But before entering into the details of this phase of the problem I shall first turn to examine a few of the simplest criteria that we can use in observing normal and abnormal biotonus pendulation in the human.

At the root of all *dis-ease* is air hunger. As long as cells are adequately supplied with oxygen, we have little dysfunction. Even the acute clinical picture in the various allergic manifestations is basically associated with local anoxia—brought about with changing tone of smooth muscle (spasm) or by changes in cell permeability and the coincident stasis that is thereby entailed.

It requires no elaborate apparatus to follow the state of the normal



biotonus of the body as reflected in air hunger. We can make use of a simple breath-holding test. This, when determined at the same time of the day in day-by-day sequence, will provide an excellent criterion of the organic state.

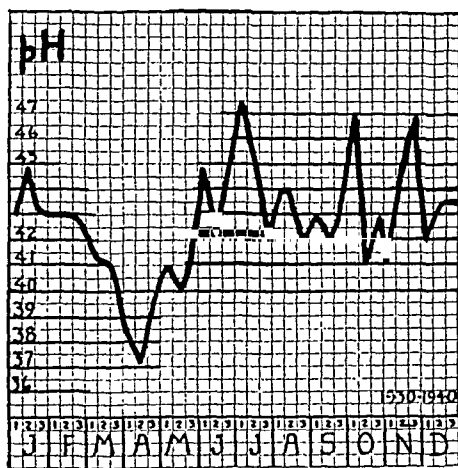


Fig. 1. Curve of pH levels of the venous blood of the arm, made in day-by-day fashion for the period 1930-1940. Note the characteristic lowering of level to its April decline to relative acidity and the sharp increase in summer and autumn.

We can use the blood pressure in a similar manner. Or any other test that we may wish to employ—the pH, the sugar level, the skin reaction, the dark adaptation of the eye, the circumference of the leg or the ability of the subject to suspend his body from a bar.

#### SEASON

We will return to the effect of season, using blood pH as a criterion. The curve of the mean annual blood pH curve from our human material for the decade 1931-1942 is illustrated in Figure 1. The pH declines to a low level in April; in the summer and autumn this is reversed. This is a basic biochemical tide that will find reflection in every physiological and pathophysiological reaction pattern.

If for instance we take blood pressure readings (Fig. 2) at the same time each day in an old woman (with vascular sclerosis) living quietly in a hospital ward, with no alteration of environment other than that associated with weather, it will be noted that there are wide changes from day to day. For instance, pressure may reach 240-250 on some days, on others 150. The seasonal tide is well defined. In the summer the pressures are lower (peripheral dilatation) (*S*), rising in the autumn (*A*) to a crest late in December. Then in January there is an abrupt decline (*J*). But while the decline in summer was a normal response to an environmental situation when peripheral vessels dilated with warm weather (*S*), the decline in January was the result of a totally different mechanism. The great pressor crests in December resulted in anoxia, the production

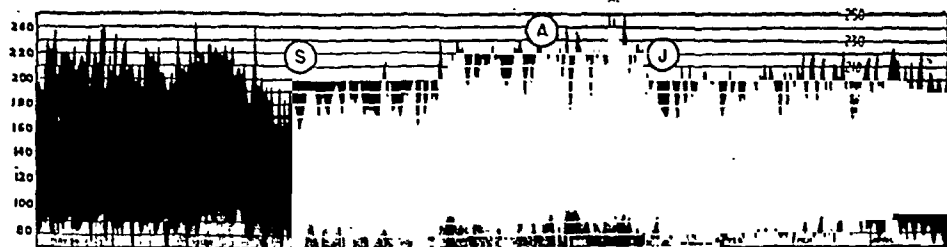


Fig. 2. Daily systolic and diastolic blood pressure readings on subject M., May, 1934, to May, 1935.

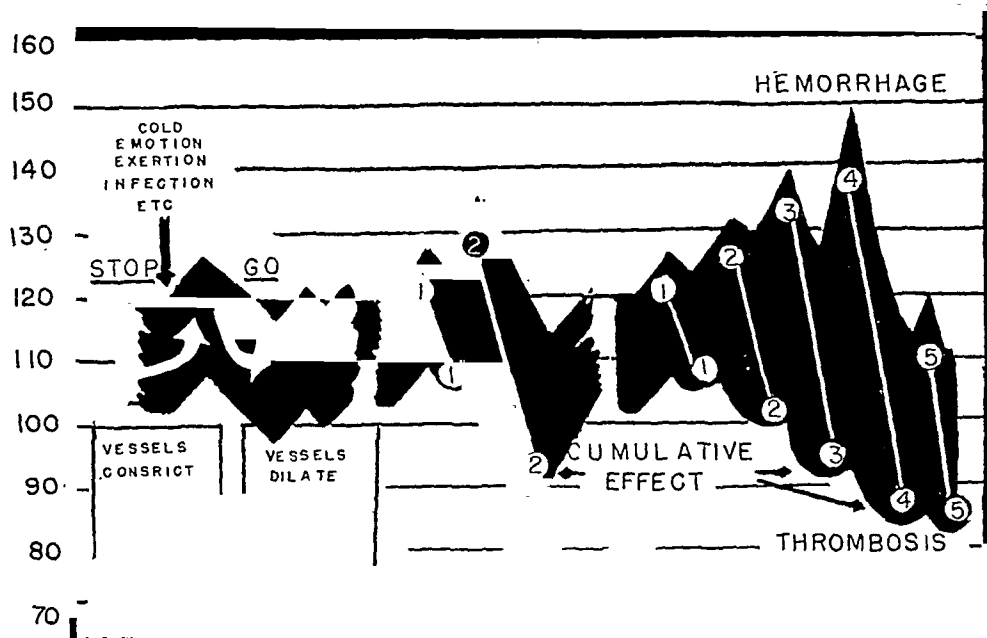


Fig. 3. Schematic reaction pattern.

of capillary active substances and the vascular tissues (smooth muscle, endothelium) became fatigued. But these are seasonal effects—their import for the allergic reaction might seem obvious.

*A Schematic Illustration.*—This organic rhythm can be illustrated very simply if we merely diagram blood pressure levels, as in Figure 3. At the arrow an energy impact occurs—it may be cold, an emotional upset, exertion, infection, an allergen. A sympaticotonia follows—vessels constrict, pressures rise—it is an “alert” or an “adrenal” phase, if you so wish to designate it. Selye termed it the “alarm reaction.”

If at this time the skin is tested, flares are negligible; there is greater resistance to infection—cells are temporarily less permeable. A relative alkalosis and hyperglycemia exist, together with an increase in blood pressure.

This “adrenal” or “stop” phase goes over to the “go” phase—vessels

dilate—there is relative acidity—cells become more permeable—they are less resistant to injury—skin flares are exaggerated.

All this is very simple. Assume now that we must equilibrate two such impacts in rapid succession (*1 and 2 in the central diagram*). Then the pressor level will be higher and also lower, and if after (*2*) another factor, such as undue heat supervenes, then the pressure may fall to unusually low levels. Or, if with seasonal accentuation, a series of impacts supervene in rapid succession, then we will face the situation in the third diagram—with periods of great pressure crests and depressions in close sequence.

What has been illustrated here for blood pressure holds for every component in the complex series of organic balances.

Allergic phenomena are characterized by sudden changes in the state of the circulation. With this come local sensory phenomena (itching, flushing and pain), then effusion and swelling, then the general expression of disturbance in the blood distribution between the skin and the splanchnic area. Primarily the effect is on the capillary endothelium—then the associated changes in the autonomic (endocrine—nervous—chemical) tone—with reflections in the major organs—stomach, liver, kidney, spleen, the bone marrow, et cetera.

If an allergic reaction takes place when the organism is in the phase of a low pH (the winter-spring status), with the implication of stimulation or fatigue—with buffers exhausted, calcium and lipoids depleted, blood pressures low, it is but logical to expect that reactions that involve capillary permeability will be accentuated. The autumn status may reverse the picture and lessen the allergic reaction that depends on the capillary mechanism.

If, on the other hand, the particular allergic manifestation involves undue smooth muscle contraction (vascular spasm, or spasm of the bronchus or the gut) then we will find a reversal of this seasonal picture—such allergic phenomena will tend to be accentuated in the summer and autumn and diminished in the spring.

And if, in the allergic mechanism, both mechanisms are involved (that is, an interplay of changing vascular permeability, together with smooth muscle relaxation and spasm) symptoms may be accentuated “at the change of the seasons”—that is, in the spring and autumn. This is by no means an uncommon phenomenon in the allergic states not directly associated with the pollens. This effect of season in altering the “state” of the organism becomes dramatically apparent in asthma, in tuberculosis, in ulcer, in migraine, et cetera.

Keeping this seasonal pendulation in mind we must extend our survey to include shorter disturbance of the balance, as well as longer cycles that will extend over the years. Shorter disturbances are commonly the reflection of air mass change—of weather. These air waves set up organic pendulations that may be of short duration, but of great amplitude. There

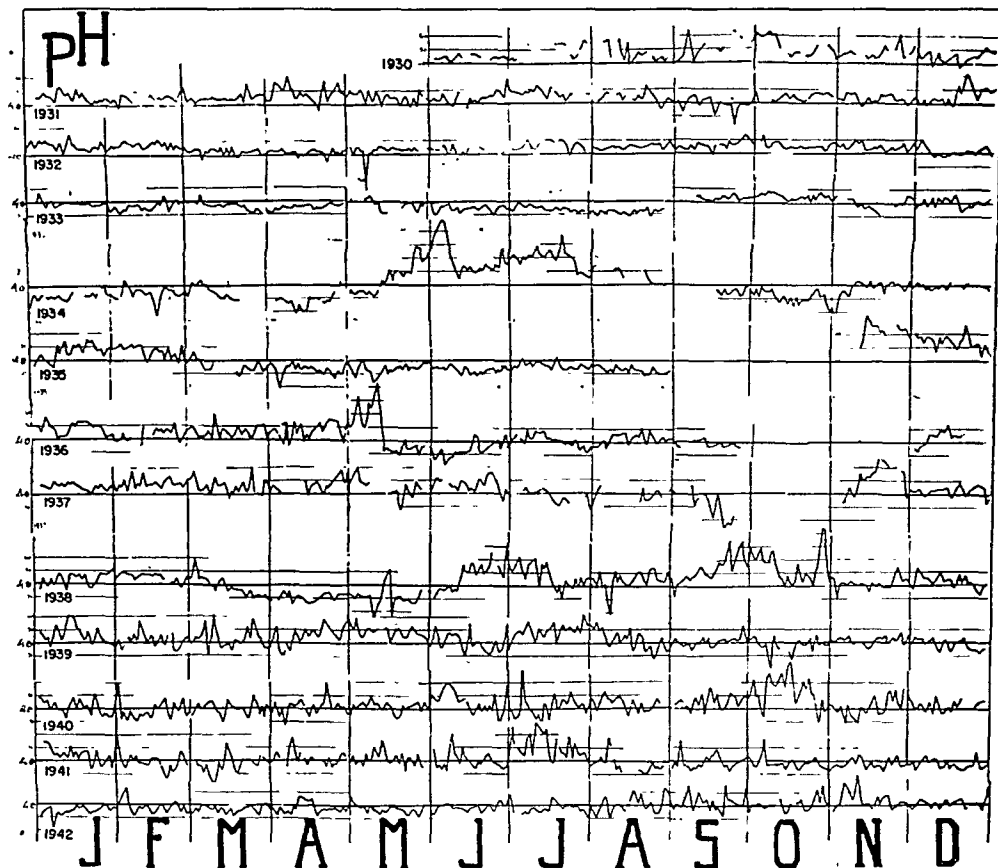


Fig. 4. Blood pH levels, 1931-1942.

is a diurnal cycle; there are cycles of a week, and longer cycles that are related either to the lunar period, or to the solar day (i. e., the rotation period of the sun), as well as the long climatic cycles that may be related to sunspot periodicity or to the amplification of such rhythms.

If we determine the pH levels for the period 1931-1942 (Fig. 4), there is indication that a long range chemical cycle of this type does occur in the human population. For the allergist this would mean that allergic responses would differ in certain years—the vegetation (and so the dosage of allergenic agents) will also differ with such climatic cycles.

The graphs present day-by-day determinations of blood pH levels of from three to five patients each day (normal or ill with relatively minor disturbance). Note the relative stability of the curves in 1932-1933 (a period of least solar disturbance) and the wide deviation in the years that follow. In 1934, for instance, an alkalotic peak occurred with the great drought and heat period (May and June). In 1936, we have an opposite situation—an alkalotic crest in early May, followed by a sharp decline in the latter part of May and June. Each year reveals a pattern of its own.

Obviously, an allergen in contact with sensitized tissue in early June, 1934, will elicit a different reaction than when in contact with the same

tissue in June, 1936. But such wide swings may occur in short intervals, as becomes evident in examining the graph.

The allergist is quite well aware of this change in the status as it affects his skin-testing methods. On some days all of the reaction flares and wheals will be large—on other days negligible. In the parlance of practice he deals with a “hot” skin or a “cold” skin. And that is a true evaluation, for at certain times the smooth muscle of the peripheral vessel is in a spastic state and vessels will not dilate—at other times will dilate readily. But he is apt to forget that it is not only true of his skin testing—it is a criterion of what is going on at the focus of clinical disturbances! The “organic state” is never the same, even if the dosage and character of the impact (in this case the allergen) is the same.

Before proceeding I would stress one more point. The allergic reaction, involving cellular responses that are also called into play by non-specific energy impacts (from which they differ mainly in speed and amplitude of response) can precipitate clinical pictures that are identical with those due to a wide variety of other forces that cause autonomic dysequilibration, for instance, an appendicitis, a colitis, a paroxysmal tachycardia, a coronary episode, a migraine. But that does not justify the myopic assumption that every appendicitis, every colitis, every tachycardia or coronary spasm or migraine has its origin in a specific allergic reaction.

The allergist must be a physician who evaluates his special field in the much wider framework of the general principles of reaction to environment, not merely reaction to a specific allergen, with disregard of all other effectors. I would again refer to Henderson's paper in which he traced the same fallacy during the bacteriological era. It was a period of oversimplification. Bacteria plus human spelled disease. Today we know that bacteria plus the kind of human—plus the state of the human (and that means time and place—food and work—sunshine and weather—season—sex) present an equation which may mean disease. A similar situation holds true for the allergic factor in disease.

Doctor Dutton has published an interesting study in which he incriminates an allergic factor in the onset of appendicitis. I am of the opinion that an allergic factor may play a rôle in appendicitis. But that by no means implies that specific allergy is *the* cause of appendicitis. Years ago we ascribed the cause to bacteria. Of course, bacteria invade the wall of the appendix, but those self-same bacteria were in and about the appendix for years and no appendicitis occurred until the “state of the tissues” was so changed that bacteria could invade. An allergic disturbance of the autonomic equilibrium can so change the state of the organism that the appendix may become the seat of inflammation, but any other major energy impact can bring about a similar situation—heat or cold, emotional or physical trauma, an infection, an intoxication, a sudden endocrine unbalance.

Inasmuch as this organic tide is (1) a factor in the precipitation of all clinical episodes and (2) uniform in its character, irrespective of the particular energy impact that has brought it into play (temperature change—emotion—trauma—allergen, et cetera) it will be useful to present a detailed examination of the more obvious manifestations.

The primary effector in all tissue regulation is air hunger and was so recognized by the Greeks. Air hunger occurs when there is vasoconstriction (*i. e.*, a phase of smooth muscle contraction) or vasodilatation (a phase of capillary dilatation and stasis). Hippocrates put it succinctly, "So in one place it stops, in another it passes sluggishly, in another more quickly. The progress of the blood through the body proving irregular, all kinds of irregularities occur."

The organic tide that I have been discussing is the reflection of this changing oxygen potential. At some times the body is air hungry, at other times has a relative oxygen plethora. In the simplest of fashions we can determine this by merely determining the breath-holding time. When taken each day at the same time it provides us with an excellent criterion of the organic state. How useful, I can best illustrate by the observations in the following case.

#### THE ORGANIC TIDE OF ANOXIA

Thrombosis occurs when the blood pressure is low, the current sluggish, the vessels adhesive and the clotting time shortened. At present more than one-third of all doctors die from coronary thrombosis, a proportion that will increase.

Coronary thrombosis is a reflection of the organic pendulation or tide that I have been discussing.

The organism first passes through a period of *increased vascular tone*. This is most commonly associated with undue environmental cold, often with increased activity, excitement, trauma, et cetera. During this phase the tissues become relatively air hungry. Capillary active substances are then formed (histamine and histamine-like substances, intermediary acid products of anoxiobiosis, carbon dioxide, et cetera), which all lower the blood pressure level and dilate the capillaries. With this the phase of increase in blood pressure shifts to one of lower blood pressure. Capillary and venous endothelium become more adhesive; the clotting time is shortened. This transition from high to low pressure may occur in a very short time (one or two days) or may reach its maximum in the course of ten days.

Now, if in this organic state of relative acidosis, of lower vascular tone, of shortened coagulation time, an environmental situation develops which would further lessen vascular tone (sudden warm weather or a mental depression or physical fatigue) then pressure levels may sink to critically low levels in regions of the body where vessels are unduly adhesive and during a time when coagulation is accelerated—then coronary thrombosis!

H. I., pharmacist by training, scientist by aptitude, allergist by preoccupation, suffered from a clinically well-defined coronary thrombosis on September 18, 1942.

Let us look at the record in this case. Figure 5 illustrates merely the maximum and minimum temperatures of the time in silhouette, the barometric pressure in

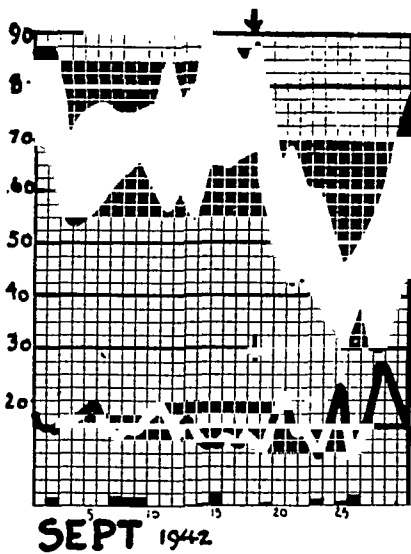


Fig. 5. Meteorogram, Chicago, 1942. Upper Curve—Maximal and minimal daily temperatures. Lower Curve—Barometric pressure. Arrow—Day of coronary attack.

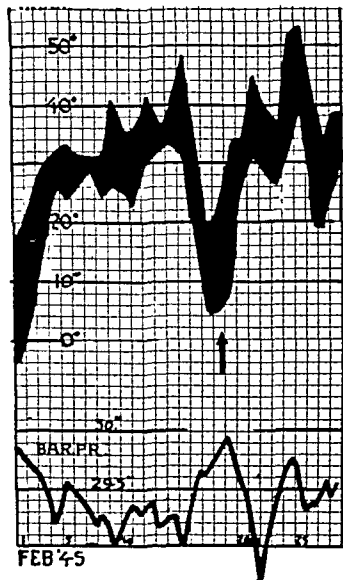


Fig. 7. Meteorogram, February, 1945. Arrow—Death.

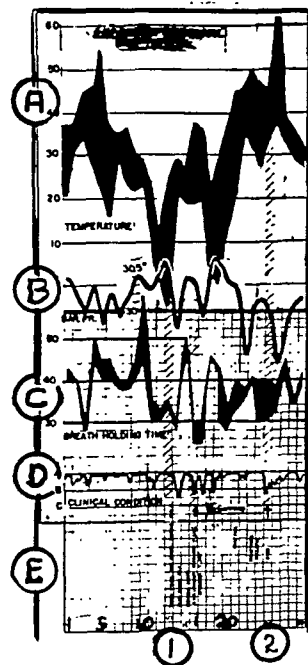


Fig. 6. February, 1944. Curve A.—Daily maximum and minimum temperatures. Curve B.—Barometric pressure. Curve C.—Breath-holding time. Curve D.—Subjective state. Curve E.—Illness notes of S. G. (1) Illness (virus pneumonia) began. (2) Death.

heavy trace and rainfall in black bars at the date line. It will be observed that it had been hot at the beginning of the month, then followed two periods of relative cold (the last on the 13th), then a sudden shift to high temperatures. With the final heat crest on the 19th (temperature 88°, barometric pressure lowered) the subject developed his coronary attack. In addition to the reaction demanded by

the changing physical environment, he was mentally depressed at the time. He made a fair recovery after the acute episode and was able to continue his activities in some measure, though painfully aware of the cardiac deficiency, and with periods of greater or less distress.

He became much interested in determining the cause of these periods of clinical distress and began to make daily recordings of weather change, of his state of well-being(*D*); his breath-holding time(*C*). This latter varied from less than thirty seconds on days of greatest discomfort, to more than sixty seconds when he "felt better." In Figure 6 his record is graphed for the month of February, 1944. The upper silhouetted curve is the daily maximal and minimal temperature(*A*). This, it will be observed, varied from a maximum over 60° on the 26th, to a low of -5°F. on the 13th.

The subjective state is indicated in the curve "clinical condition(*D*) and there are clinical notes concerning S. G. of Chicago, (*E*) a mutual friend. Observe that by the 11th his subjective condition had declined and the breath-holding time had dropped abruptly (*1*). This with the major decline in environmental temperatures from 55° to -5°F. By the 14th the decline in well-being was exaggerated. At this time S. G. became ill.

With warmer temperature H. I. felt better, and breath-holding time increased. A series of waves now followed in breath-holding time, in environmental temperature and in well-being. Finally, at the same time that the condition of H. I. became worse (25th) S. G. died(*2*) when environmental temperatures increased rapidly. Why? Because the anoxia associated with the passage of the cold wave had induced a relative acidosis, and blood pressure began to fall. This decline was accentuated with the succeeding warm weather. With this collapse and death in S. G., there was a distinct decline in the well-being of H. I. This would be a characteristically portentous situation for coronary thrombosis(*2*).

H. I. died on February 18, 1945 (Fig. 7). Here a striking polar air wave, which sent temperatures down almost to zero, was effective in throwing a greater load on a damaged myocardium, and death promptly followed.

Environmental rhythms of this character are continually effective in initiating corresponding biochemical and biophysical rhythms, as the human organism seeks to adjust to the demands of the environment and it is this change in the organism from day to day which the allergist must evaluate in the varied symptomatic picture of his patient.

#### THE IMPLICATIONS FOR THE ALLERGIST

Quite apart from the day-by-day and seasonal change in reactivity of the organism to an established allergy a number of other phenomena must be considered as they become evident in the changing clinical picture.

With the shift in the blood mass from the periphery to the splanchnic area and vice versa, as the organism parries environmental impacts, sensitization of tissues will be effected.

In the first place, a skin that is active (vaso-dilatation) will present a different receptive situation than a skin that is inactive, if the allergen is by contact.

If the allergen is one that reaches the blood stream and is universally distributed, then the circulation of the allergen and the presumptive "degree" of sensitization of the tissues or organs will vary with the state of the splanchnic-peripheral balance. If, for instance, the skin vessels



are dilated while the splanchnic area is relatively poor in blood, the probability will be greater that the allergen will be absorbed in the peripheral area, endothelium, the coats of the vessel, and the connective tissues. Under such conditions, sensitization and later clinical response might be ac-

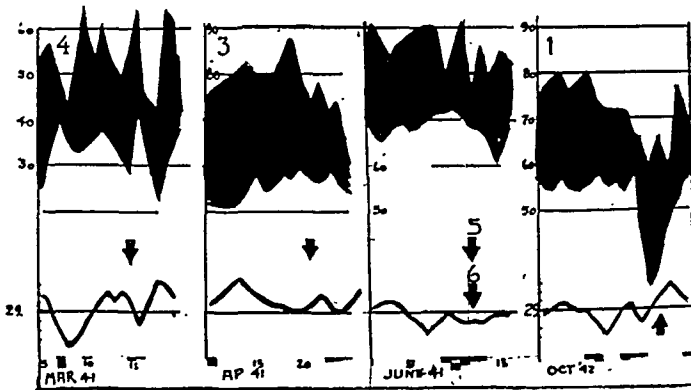


Fig. 8. Meteorogram to illustrate precipitation of jaundice following serum injection in the Beeson cases. Arrows date the association in Cases 1, 3, 4, 5, 6.

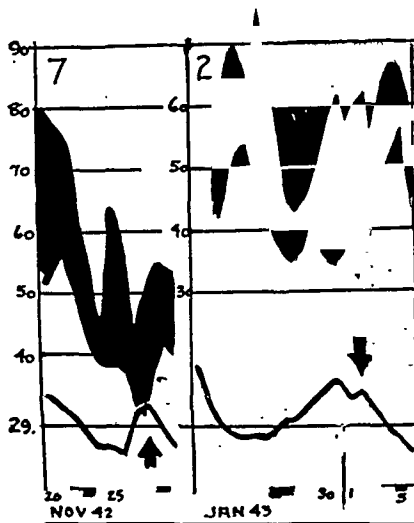


Fig. 9. Meteorogram to illustrate precipitation of jaundice following serum injection in the Beeson cases. Arrows date the association in Cases 2 and 7.

centuated in the peripheral tissues. If, on the other hand, the allergen enters the blood stream when the peripheral vessels are contracted, the opportunity for visceral sensitization will be much greater.

We have to consider another phenomenon that at first glance seems paradoxical. When patients suffering from hay fever and asthma are kept in air-conditioned (for temperature and humidity) and allergen-free chambers during the pollen season, they may still suffer severe asthmatic attacks with periods of major weather change. Dr. Tell Nelson has reported such an episode.<sup>3</sup>

I have shown that patients so confined still reveal a changing organic

rhythm that conforms to the environmental situation outside the conditioned chambers.

How can we explain such a paradox? The simplest would be the assumption that the sensitized tissues are actually more sensitive to change in the autonomic tone, irrespective of specific initiating factors. Or we might turn to a bacterial analogy. When bacteria enter the blood stream, they are rapidly picked up by the large blood filters and then rendered innocuous, or may vegetate for some time. If, now, a vascular shock occurs, bacteria so localized may again be thrown into the blood stream. We may have a related situation with the allergic phenomena. Assume that a reactive area exists in a joint membrane. The specific allergen may be inhaled or get into the blood stream in some other way. It might promptly be taken out by the liver and spleen. While held in the filters there would be no local manifestation. But if in the course of time an autonomic swing of sufficient degree would occur and with this, the "stored" allergen liberated, then a reaction might occur in the sensitized area even though the subject was in the air-conditioned chamber.

I shall illustrate an analogous situation using a series of case records of Beeson.<sup>1</sup> Beeson described jaundice occurring in army recruits from one to four months after the transfusion of blood or plasma, and dated seven cases when jaundice suddenly appeared.

I have prepared six small meteorograms of the time to illustrate the environmental situations. In these, the maximum and minimum daily temperatures are indicated in the black silhouetted field, and the case number is indicated. The barometric pressure is the heavy trace below—the precipitation by the black bars at the date line. The arrow points to the day of onset (Figs. 8 and 9).

The jaundice occurred when temperatures had declined as indicated:

*Case 1.* 80° to freezing.

*Case 2.* 75° to freezing.

*Case 3.* 88° to 56°.

*Case 4.* 65° to freezing.

*Cases 5 and 6* (simultaneously!)

90° to 70°—at a period of severe rain for a week.

*Case 7.* 80° to freezing.

(For the seven cases, barometric pressure increased from 28.93" to 29.1" for the five days before the attack of jaundice.)

In these cases we are presumably not dealing with a specific sensitization; we are dealing with an altered state of the bile capillaries or of the parenchyma, and the altered state does not reach clinical significance until an environmental impact of magnitude so altered the biochemical state of the individual that local adjustment was inadequate and symptoms appeared.

Such changes in the reactive state are of importance in evaluating the allergic phenomena.

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## PENICILLIN URTICARIA

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THE release of penicillin for civilian use has verified earlier reports on the frequency of urticaria resulting from penicillin therapy. Lyons<sup>4</sup> states that this complication developed in 5.7 per cent of 209 patients treated with penicillin. Anderson and Keefer<sup>1</sup> give its incidence as from 2 to 5 per cent. Criepp<sup>2</sup> concluded that the urticaria is probably unrelated to penicillium spores. Feinberg<sup>3</sup> was unable to demonstrate penicillin sensitivity by means of skin tests of a group of patients showing positive skin reactions to extracts of penicillium spores. Lyons states that patients having penicillin urticaria do not develop urticaria following subsequent courses of penicillin, and that the period of sensitivity to penicillin is remarkably transient. He states further that cutaneous and ophthalmic tests during and after the reactive phase are negative. This is in direct variance with the findings of Criepp, who obtained both positive intradermal skin tests and positive passive transfer in the presence of penicillin urticaria.

The following case coming under my observation seems worthy of record because of changes in the skin responses which may explain the apparent discrepancies in previous reports on penicillin urticaria:

### CASE REPORT

A white woman, thirty-five years of age, entered the hospital May 25, 1945, with acute serofibrinous pleuritis. She gave no history of allergy, but stated that her maternal grandmother had asthma. Her past illnesses included chickenpox, mumps, and whooping cough. Blood studies on May 25 revealed 3,680,000 red blood cells, 21,900 white blood cells, 2 per cent eosinophils, and a sedimentation rate of 31. On June 19 there were 3,950,000 red blood cells, 7,600 white blood cells, 2 per cent eosinophils, and a sedimentation rate of 6. Thoracentesis disclosed a clear straw-colored fluid with occasional pneumococci and short-chain streptococci, 34 per cent polymorphonuclears, 16 per cent lymphocytes, and no eosinophils.

Penicillin was administered every three hours in doses of 25,000 units. Urticaria developed on June 19, appearing first on the face and neck and becoming generalized in a few hours. With each succeeding dose of penicillin the urticaria became more severe, and on June 20 the administration of penicillin was stopped. Severe urticaria persisted for three days more. On June 25, five days after the penicillin therapy was discontinued, the skin was again normal.

Studies were then conducted to determine the least amount of penicillin that would produce the urticaria; the component of penicillin responsible for the reaction; and the skin and ophthalmic responses to each component. The findings of these studies are presented in the tables.

Table I shows that during the reactive phase from June 19 to June 30 as little as 50 units of commercial penicillin sodium produced urticaria, whereas after this period the injection of increasingly high doses up to 20,000 units caused no reaction whatever. Significantly, also, injections

# PENICILLIN URTICARIA—ZELLER

## TABLE I. URTICARIAL RESPONSE TO VARIOUS DOSES OF PENICILLIN COMPONENTS\*

Date	Penicillin component	Effect
June 20	5,000 units of commercial penicillin sodium.	Diffuse itch in 30 minutes, generalized urticaria in 1 hour, persisting to next day.
June 20	500 units of commercial penicillin sodium.	Diffuse itch in 25 minutes, generalized urticaria in 1 hour and 15 minutes, persisting 4 hours.
June 30	50 units of commercial penicillin sodium.	Diffuse itch in 25 minutes, generalized urticaria for 1 hour.
July 2	5 units of commercial penicillin sodium.	No effect.
July 3	416 units of crystalline penicillin sodium.	No effect.
July 4	832 units of crystalline penicillin sodium.	No effect.
July 5 a.m.	1,666 units of crystalline penicillin sodium.	No effect.
July 5 p.m.	3,200 units of crystalline penicillin sodium.	No effect.
July 6	2,000 units of commercial penicillin sodium.	No effect.
July 7	2,000 units of impurities of commercial penicillin sodium.**	No effect.
July 9	20,000 units of commercial penicillin sodium.	No effect.

\*Crystalline penicillin sodium and impurities of commercial penicillin sodium made available through the courtesy of the Abbott Laboratories.

\*\*Impurities of commercial penicillin sodium have not been identified.

## TABLE II. IMMUNOLOGIC RESPONSE TO PENICILLIN COMPONENTS\* AND PENICILLIN EXTRACT

Substance used	Intradermal tests	Control intradermal test	Ophthalmic test	Passive transfer
Penicillium extract, June 26, July 6, July 11	Neg.	Neg.	Not done	Not done
Commercial penicillin sodium (5,000 units per c.c.), June 26	Pos.	Neg.	Neg.	Pos.
Crystalline penicillin sodium (1,666 units per c.c.), July 6	Neg.	Neg.	Neg.	Not done
Impurities of commercial sodium penicillin (2,000 units per c.c.), July 7	Neg.	Neg.	Neg.	Not done
Commercial penicillin sodium (5,000 units per c.c.), July 9	Neg.	Neg.	Neg.	Neg.
Impurities of commercial sodium penicillin (2,000 units per c.c.), July 11	Neg.	Neg.	Not done	Neg.
Crystalline penicillin sodium (1,666 units per c.c.), July 11	Neg.	Neg.	Not done	Neg.

\*Crystalline penicillin sodium and impurities of commercial penicillin sodium made available through the courtesy of the Abbott Laboratories.

of crystalline penicillin sodium and impurities of commercial penicillin sodium failed to produce urticaria after June 30. It is possible that if skin tests and passive transfer had been done with crystalline penicillin sodium and impurities of commercial penicillin sodium before June 30 the component responsible for the urticaria might have been determined.

(Continued on Page 394)

# INHALATION OF TEN PER CENT CARBON DIOXIDE AND NINETY PER CENT OXYGEN PLUS 1:100 GLYCERINIZED EPINEPHRINE HYDROCHLORIDE FOR THE RELIEF OF ASTHMATIC ATTACKS

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THE medical profession now recognizes that severe paroxysms of asthma and coughing are often relieved by the inhalation of 1:100 solution of suprarenalin hydrochloride.

It is also well known that 1:100 suprarenalin hydrochloride exerts a drying effect, often increases the cough reflex, and is also irritating to the mucous membranes.

To control the irritation of the mucous membranes following the use of the solution 1:100 suprarenalin hydrochloride, the use of glycerin in hot water orally was advocated immediately after the patient used this form of therapy for the relief of paroxysms of asthma and coughing. In 1943 the author<sup>5</sup> published a formula and method for the preparation of 1:100 glycerinized suprarenalin hydrochloride. Several large pharmaceutical houses now employ this formula or modifications of it, in the manufacture of glycerinized suprarenalin for oral inhalation. The formula is as follows:

Suprarenalin crystals	10.0 gms.
Sodium chloride	9.0 gms.
Chlorobutanol	5.0 gms.
Sodium bisulfite	0.9 gms.
Dilute HCl (10% U.S.P.)	20.0 c.c.
Glycerin	50.0 c.c.
Distilled water, to make	1,000.0 c.c.

Eight hundred fifty cubic centimeters of triple distilled water and 50 c.c. of glycerin are heated to boiling to remove the dissolved air. The heat is shut off, and the chlorobutanol and sodium chloride are added. The solution is cooled to room temperature, and the sodium bisulfite is added.

Ten grams of suprarenalin crystals are dissolved in 20 c.c. of 10% HCl and added immediately to the above solution.

The pH is then adjusted to 3.0 (a fluctuation from 2.9 to 3.1 is permissible). If necessary, a few drops of dilute sodium hydroxide solution may be used to bring the pH to 3.0. In case the HCl is a little weak, a small amount of normal HCl should be added.

Distilled water is added until the volume is exactly 1,000 c.c. The solution is then filtered and filled into bottles. (Avoid the use of metal apparatus in the preparation of material.)

The pure suprarenalin crystals used in making the 1:100 suprarenalin hydrochloride and also the technical data were freely furnished to the author by the Armour Laboratories, Chicago, Illinois.

Many tests were performed to insure that the glycerinized 1:100 suprarenalin solution retained its stability. Various batches were exposed to room temperature, stored in refrigerators, exposed to sun, stored in closets along with unglycerinized suprarenalin hydrochloride. The amount of discoloration present at the end of two, four, and six months was slightly less in the glycerinized material than in the unglycerinized.

It was also decided to vary the percentage of glycerin present in the formula. Various batches were made up that contained 5, 8, 11, and 15 per cent glycerin. These solutions were then tried in various vaporizers. It was found that if the open end of the vaporizer was held about four inches from a clear vertical piece of glass, the 5 and 8 per cent solutions produced the largest ring of vaporized solution on the glass.

The volume of solution expelled per minute from the end of the vaporizer was also measured. This was determined by attaching a saddle, hose and vaporizer to a small tank of compressed air, and then placing measured amounts of the 5, 8, 11, and 15 per cent glycerinized 1:100 suprarenalin hydrochloride in the vaporizer. The flow of oxygen through the hose was also controlled. As the percentage of glycerin per volume increases so the amount of solution vaporized per minute decreases.

A simple method and technique for the continuous inhalation of 1:100 glycerinized suprarenalin hydrochloride was published by the author in the article referred to above. The method is as follows: Use a small pressure tank of oxygen with the usual reducing valve to regulate the flow. An outflow tube is attached from the tank to a vaporizer, and oxygen is introduced at a flow sufficient to produce adequate vaporization. A flow of four to seven liters will vaporize 1 c.c. of solution in from three to ten minutes. When this method is used, the patient merely holds the nozzle of the vaporizer in his oral pharynx and breathes quietly. Very little additional effort is required (Fig. 1).

Richards, Barach and Cromwell stated the following advantages of this technique:

1. A larger amount of solution is brought into contact with the bronchial mucous membrane than is possible with the hand bulb.

2. This is done without effort on the part of the patient in a severe asthmatic state.

3. Solutions which are less irritating, and with milder bronchodilator action, are often effective in suppressing moderate asthmatic attacks when given by the continuous technique; whereas, they are ineffective when used with the hand spray. This is an important fact in patients who suffer from dryness and irritation of the mucous membrane of the tracheal bronchial tree, after the inhalation of 1:100 unglycerinized suprarenalin solution.

We all know that the following untoward effects often occur after the use of 1:100 suprarenalin hydrochloride, by either the continuous inhala-

tion method or the hand bulb vaporizer method: (1) dryness of the throat, (2) irritation of the throat, (3) nervousness, (4) palpitation, (5) nausea, (6) headache, (7) dizziness, (8) weakness, and (9) pallor. The appearance of these symptoms in individuals who use the hand bulb

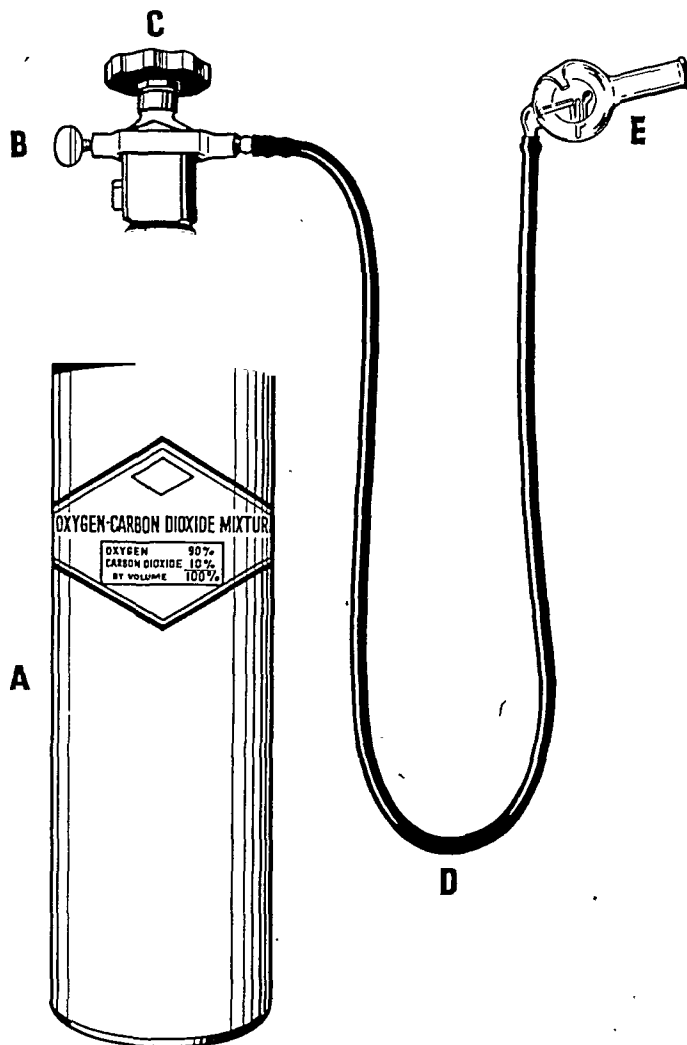


Fig. 1. *A*, Oxygen, Carbon dioxide mixture; *B*, saddle for tank (Philadelphia Surgical Instrument Company, 1717 Samson Street, Philadelphia, Pa.); *C*, handle; *D*, flexible rubber hose; *E*, vaporizer.

vaporizer is often due to frequent inhalation of unsatisfactory amounts of the solution, and to the constricting effect of the drug on the mucous membrane, which in turn, brings on dryness and irritation. Dryness and irritation of the air passages occurs less frequently when the continuous inhalation therapy is used. Abramson arrived at similar conclusions in 1940, after he had treated a group of patients for a period of several years with 1:100 epinephrine containing glycerol. Untoward symptoms occur less frequently when the glycerinized 1:100 suprarenalin hydrochloride is used in sufficient amounts to provide relief.

Holinger, Basch, and Poacher<sup>3</sup> recently published a very fine paper

on the effect of carbon dioxide on the bronchial secretions, in which they make the following statements:

"Carbon dioxide may be considered an extremely efficient expectorant. It alone reaches the deeper, very obstructive type of secretion which must be frequently and efficiently drained to prevent serious types of permanent pulmonary or bronchial damage. It is apparent that the action of carbon dioxide is in part dependent on its ability to stimulate an actual resorption of secretions. However, its most important actions are to enforce deeper, more active respiratory movements as well as to liquefy the sputum and stimulate the cough reflex. By evacuating the more dependent bronchi, sputum otherwise inert is brought to a level from which it can be coughed out easily or removed more efficiently by direct suction through the bronchoscope.

"Examination of expectorated sputum following various periods of oxygen administration showed an increase in its content of organic and inorganic substances. The extent to which these factors had been increased suggested that the action of oxygen had been one of concentration of the sputum. This was confirmed by the bronchoscopic picture. The tracheobronchial mucosa was pale or even blanched in appearance following oxygen administration, and the measured viscosity of aspirated mucus had decidedly increased over the usual measured viscosity of the aspirated mucus of the same patient without oxygen. A clinically important observation was the adherence of plaques of mucous to the bronchial walls, an observation never noted on the same patient without oxygen inhalations.

"The actions of gas inhalations are quite specific, and they grossly influence the physical and chemical qualities of both the expectorated and the bronchoscopically obtained sputum, as well as the character of the bronchial mucosa. Steam inhalation, or the inhalation of a high humidity atmosphere, results in the liquefaction of sputum. Carbon dioxide has an action quite similar to that of steam, but to a greater degree. And in addition, it increases the resorbing power of the bronchial mucosa; consequently it may be considered an extremely efficient expectorant."

Carbon dioxide 10 per cent may be used with 90 per cent oxygen in the pressure tank mentioned above, with the usual reducing valve to regulate the flow. A vaporizer containing 1:100 glycerinized suprarenalin hydrochloride is attached to a rubber outflow tube and vaporization of this material through the attached tube and vaporizer. The patient merely holds the nozzle of the vaporizer in his oral pharynx and breathes quietly.

This procedure has been employed by us twenty-eight times and the following effects have been observed:

1. Bronchodilator action takes place from the inhaled glycerinized 1:100 suprarenalin hydrochloride.

2. Dryness of the tracheobronchial tree is prevented by the use of glycerin in the solution. It also helps to raise the humidity of the inhaled air and vapor.

3. The resorbing power of the bronchial mucosa is increased.

4. The sputum is liquefied and the patient is able to expectorate more easily.

5. Long, tenacious, thick mucous plugs are often coughed up after the inhalation of 1:100 glycerinized suprarenalin by means of the carbon

*(Continued on Page 396)*



# PARENTERAL USE OF BUTANEFRIE IN ASTHMA

## A Comparison With Epinephrine

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ASTHMA is always annoying and often incapacitating; therefore it behooves us to consider any addition to our armamentarium against this ailment, which at some time or another affects two per cent of our population. The author and his associates previously reported on the pharmacology and clinical use in asthma of a new sympathomimetic drug, ethylnorsuprarenin, also known as butanefrine. Chemically it is 1-(3, 4-dihydroxyphenyl)-2-amino-1-butanol. To recapitulate briefly, injected intramuscularly or subcutaneously in approximately twice the dosage employed with epinephrine, it gave equivalent relief in asthma. Butanefrine lacked the pressor effect of epinephrine; actually the diastolic pressure was moderately lowered, with a widening of the pulse pressure and slight acceleration of the heart rate. Butanefrine did not provoke nausea and vomiting, making it preferable for use in children. No angina was produced in patients with associated cardiac or hypertensive disease, making it preferable in this group. Finally, tremor and nervousness in general was encountered less with butanefrine than with epinephrine. The asthmatics studied were mainly uncomplicated "extrinsic" cases (from externally introduced allergens).

The purpose of this paper is to report further comparisons of the effects of butanefrine and epinephrine on asthmatics, this time separating them into two groups: those of extrinsic and reflex origin uncomplicated by infection, and those whose asthma was accompanied by definite bronchial infection. The latter included cases of both intrinsic and extrinsic origin.

### FURTHER STUDIES BY INJECTION METHOD

In twenty-three more uncomplicated "extrinsic" asthmatics the clinical relief paralleled practically exactly that obtained with epinephrine; the ages of the patients ranged from four to fifty-nine years. In seventeen cases of "extrinsic" asthma complicated by bronchial infection that obtained relief from epinephrine, ten obtained the same relief, four less relief, and three none at all; the ages ranged from twelve to sixty years. In a group of twenty "intrinsic" cases (all with negative skin tests and with varying amounts of bronchial infection) one obtained more relief, twelve approximately the same relief, four cases less relief and three cases no relief. The ages of this last group ran from thirty-one to sixty-four years. Dosage employed was 1 mg. butanefrine per 45 Kg. (100 pounds) body weight, twice that of epinephrine. The subcutaneous route was employed. The same lack of angina and nausea was noted in these

TABLE I.

LUMEN-INCREASING EFFECT	EFFECT POSSESSED BY EPI- NEPHRINE	EFFECT POSSESSED BY BUTA- NEFRINE	RELATIVE IMPOR- TANCE OF EFFECT IN UNCOMPLI- CATED EX- TRINSIC AND REFLEX ASTHMA	RELATIVE IMPOR- TANCE OF EFFECT IN ASTHMA WITH BRONCHIAL INFECTION
1. Relaxation of bronchiolar smooth muscle spasm	*	*	****	***
2. Lessening of vascular bed of mucosa through vasoconstriction	*	—	**	***
3. Lessening of mucosal edema by diminution of the arteriolar-venule pressure differential	*	—	**	**
4. Lessening of mucosal edema due to improved lymphatic drainage allowed by relaxation of broncho-spasm	*	*	***	**
5. Lessening of secretion indirectly thru constriction of vessels supplying mucous glands and epithelium	*	—	*	***

cases as in the original report, and the same diminution of tremor and nervousness as compared with epinephrine.

#### MECHANISM OF ANTI-ASTHMATIC ACTION AND COMMENT

Leaving side actions out of the picture and confining our attention strictly to the relief of asthmatic respiration, it is apparent that whereas epinephrine and butanefrine are equally effective in the purely extrinsic (and reflex) asthmas, when the element of infection enters butanefrine becomes relatively less effective. The explanation of these facts becomes apparent when the mechanism of the bronchial-lumen-increasing actions of these two drugs are considered. The accompanying table needs no amplification. It can be seen that epinephrine, because of its added vasoconstrictor effect, has the balance tipped in its favor when infection is present but in uncomplicated cases this factor is negligible.

Because the vasoconstrictor action of epinephrine limits its own absorption, the effect is apt to be more prolonged than the effect of butanefrine, which does not limit its own absorption. However, the use of butanefrine is much safer for emergencies intravenously because of this lack of pressor effect. To delay the absorption of butanefrine and thus prolong its effect, five to ten per cent of epinephrine solution can be mixed right in the syringe with butanefrine for intramuscular or subcutaneous injection. Ultimately such measures for prolonging the action of epinephrine as suspension of the hydrochloride in gelatine or the base in oil will be tried with butanefrine.

## USE OF BUTANEFRINE IN "CARDIAC" ASTHMA

During the course of these investigations butanefrine was tried on four cases of "cardiac" asthma. There were no adverse effects and only questionable beneficial ones. Administration of morphine, after no effects were apparent from the butanefrine, gave characteristic excellent relief of symptoms. Neither a cardiologist nor an allergist usually has much difficulty in distinguishing between cardiac (three per cent) and bronchial (ninety-seven per cent) asthma. However, a general practitioner frequently may be at a loss, and he is faced with a therapeutic Scylla and Charybdis. Although epinephrine benefits asthma it has an adverse effect upon cardiacs and hypertensives, particularly those with coronary artery disease. Morphine is of immense benefit in the cardiac cases but it is usually dangerous and sometimes fatal in bronchial asthma, since it inhibits bronchiolar peristalsis and the cough reflex, allowing patients to drown in their own secretions. With butanefrine at hand, however, one can obtain relief in bronchial asthma without endangering the cardio-vascular system. In other words, one does not have to take chances with a therapeutic trial when he is using butanefrine.

## SUMMARY

1. Butanefrine 1:500 and epinephrine 1:1000 hypodermically are equally effective in relieving asthma of purely reflex and extrinsic origin in the absence of bronchial infection.
2. The effectiveness of butanefrine is relatively less when bronchial infection is present.
3. The vasoconstrictor effect of epinephrine which is lacking in butanefrine accounts for the greater effectiveness of epinephrine in infected cases.
4. Angina, nausea and pressor effects are entirely lacking with butanefrine. Tremor and nervousness occur less frequently and with less severity with butanefrine than with epinephrine.
5. Therapeutic trial in asthma which may be of cardiac origin is safe with butanefrine.

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The Butanefrine used in these investigations was supplied through the courtesy of the Winthrop Chemical Company.

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*An Unusual Case of Sulfathiazol Sensitivity of the Renal Type.* Peters, John and Koven, A. J.: *Ann. Allergy*, 2:230, 1944.

Case report revealing anuria following the use of sulfathiazol, total 14 grams. No crystallization or tubular concretion was found on cystoscopy and ureteral irrigations. Authors believe this is true sensitivity, acting on the renal tissue.

# AN UNUSUAL EFFECT OF AMINOPHYLLINE ON THE INTESTINAL TRACT

## Case Report

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THE object of this case report is to record observations on the effects of aminophylline on the intestinal tract and to suggest that aminophylline may be useful in the diagnosis and treatment of the allergic bowel.

The patient was a woman forty-two years of age with a history of bronchial asthma and hay fever of fifteen years' duration, intestinal distention, attacks of nausea and vomiting for eighteen years, and frequent headaches. Appendectomy fifteen years ago and cholecystectomy a year later failed to relieve the abdominal symptoms. Two additional laparotomies in the last ten years, performed for intestinal obstruction, resulted in no relief of the intestinal symptoms except the acute episodes. Two of the patient's sisters had bronchial asthma. Skin tests of the patient revealed reactions to grass and ragweed pollens and to dust. In addition, ingestion tests disclosed sensitivity to a number of foods, manifested by abdominal distention and pain.

During the ragweed season of 1944 the patient developed asthma, for which aminophylline, grs.  $7\frac{1}{2}$ , was given intravenously. Not only was the asthma relieved, but at the same time the abdominal distention, which fairly simulated a seven-month pregnancy, disappeared. On subsequent occasions aminophylline was injected for the relief of uncomplicated abdominal distention causing distressing pain and discomfort. Before the injection of the aminophylline, measurements of the abdominal circumference taken at the level of the umbilicus and the costal margin at the level of the eighth rib were 40 inches and 31.5 inches, respectively. Measurements taken ten minutes after the injection at the same levels were 36.5 inches and 30 inches, respectively, a difference of 3.5 inches at the umbilical level and 1.5 inches at the costal level. At the same time there was complete relief of the abdominal distention, pressure and pain. This effect was observed repeatedly on subsequent injections, but particularly during an episode when all symptoms of acute intestinal obstruction developed. The usual intubation, enemas, and other palliative measures failed to relieve the obstruction. The intravenous injection of aminophylline, grs.  $7\frac{1}{2}$ , produced complete relief of the formidable picture of intestinal obstruction within ten minutes. Epinephrine given hypodermically and aminophylline given orally in doses as high as 25 grs. a day produced no relief of abdominal symptoms; in fact, aminophylline given orally in doses exceeding 8 grs. daily increased the abdominal cramps.

X-ray studies were undertaken to determine the site of action of the aminophylline. Flat scout films before the injection revealed an air-filled descending colon and caecum with outward convexity of the descending and ascending colon, the former measuring 3.5 cm. in width at the iliac crest. Five minutes after the intravenous injection of the aminophylline the descending and ascending colons were displaced medially with the convexity directed medially and the descending colon measuring 6 cm. at the iliac crest. One and a half hours after the ingestion of barium and before the injection of aminophylline, roentgenograms revealed a feathery structure of the jejunum with clumping of the ileum and outward convexity of the ascending colon. Five minutes after the intravenous injection of  $7\frac{1}{2}$  grs. of aminophylline, roentgenograms revealed rapid filling of the ascending colon with medial displacement and straightening of the convexity, and clumping of the ileum giving way to definite looping.

Roentgenograms made before and after the intravenous injection of aminophylline revealed no apparent effect on the gall bladder previously outlined with Priodex.

Askanazy<sup>1</sup> introduced the theobromine salts for the relief of cardiac dyspnea in 1895. Efron,<sup>3</sup> who in 1936 was the first to use aminophylline for the relief of bronchial asthma in the United States, stated that Van Leewen originally suggested the drug for this purpose in 1933.

Aminophylline has been used effectively also for the relief of biliary colic,<sup>2,6</sup> but I have been unable to find any previous report of an effect exerted by it on the gastro-intestinal tract except that of Huidobro, Montero, and Cuevas,<sup>4</sup> who observed that, in normal man, theophylline ethylenediamine acted like amyl nitrite on the jejuno-ileum, but less intensely and for a longer period of time.

The site of action of aminophylline in bronchial asthma has been variously ascribed to medullary stimulation of the respiratory center,<sup>5</sup> stimulation of the central nervous system, and its direct action on the bronchial musculature<sup>7</sup> producing relaxation of the contracted circular muscle. The mechanism of action in biliary colic has been thought to be the antispasmodic action of the drug on the musculature of the biliary tract<sup>2,6</sup> and perhaps, in addition, on the gall bladder. My own observations fail to reveal any action on the gall bladder.

The case reported herewith points to an antispasmodic effect of aminophylline on the allergic bowel indicated by the roentgenograms and clinical response. The collapse of the abdomen as noted by measurements is somewhat paradoxical for there was no passage of flatus at any time. It is suggested that the explanation may have been a redistribution of the gas in the bowel. The frequency of abdominal symptoms in the allergic individual is well known although their mimicry of the acute surgical abdomen is not always recognized. It is suggested that aminophylline administered intravenously may not only offer diagnostic differentiation under these circumstances but also relieve the allergic bowel.

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# Editorial

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## THE FUTURE OF AMERICAN MEDICINE

Apart from a postwar labor civil war, one of the most serious problems confronting us and which involves both the medical profession and the public is the threatened enactment of the Wagner-Murray-Dingell Bills introduced into Congress May 24, 1945. Of The 185 pages of these bills, 183 are given to exhortation, propaganda, provisions, and benefits. The remaining two pages are devoted to assessing ten billion dollars annually for the single purpose of setting up a wholly socialistic device for the purpose of providing "Personal Health Services" for all Social Security beneficiaries and all of their dependents—110,000,000 people.

This unprecedented departure for alien collectivist control under the guise of true humanitarianism is truly more revolutionary and far-reaching than any proposals ever presented before in the United States Congress. As now proposed the bills form the basis for "Compulsory Health Insurance," which means state medicine. This political distribution of medical care if made a law would be the first important step in transforming a rapidly expanding Federal bureaucracy with totalitarian state control as its goal.

If enacted, these bills would make the Surgeon General of the Public Health Service a medical dictator, under the direction of the Administrator of the Social Security Board, a layman, to provide the services and with full authority to hire doctors, specialists, dentists, nurses, laboratory technicians, and establish rates of pay; establish fee schedules for physicians' and dentists' services; fix the qualifications for specialists; determine the number of individuals for whom any doctor or dentist may provide service; determine what hospitals or clinics may provide service for patients and under what conditions. There would be required a public record of the most intimate and sacred personal relationships of every patient. This information could be used by the curious and unscrupulous at will.

The over-all Social Security tax is to be eight per cent of wages up to \$3,600, four per cent to be paid by the employer and four per cent by the employee. Self-employed are required to pay five per cent of "the market value" up to \$3,600 of their services. The tax is five per cent for the state and local governments coming into the system, half being paid by the government unit and half by the employee. For Personal Health Services, three of the eight per cent tax, or approximately \$3,142,000,000 a year, would be provided. However, this stupendous sum is to be supplemented from the General Revenue. All payments are to be made in cash. Payments are to be made in cash when appropriating funds for the construction of hospitals and health facilities, providing grants for public health services and for maternal and child health and welfare service, as well as for comprehensive public health assistance for

the needy and to nonprofit corporations and agencies engaged in research or in undergraduate or postgraduate professional education. Workers are to be reimbursed during periods of unemployment and temporary disability. Cash payments are also made to provide monthly retirement benefits for all male workers having reached the age of 65 and female workers having reached the age of 60. Widows, mothers, parents, and dependent children of workers will receive monthly benefits. Also widows, widowers, or heirs on the death of workers will receive "Lump Sum Payments." However, *no cash payments are made* when providing Personal Health Service for all Social Security beneficiaries and their dependents.

A positive appraisal of these provisions would make the Surgeon General of the United States Public Health Service the dispenser and in complete control of all health care and the final arbiter of the physical and mental well-being of the nation. The whole procedure is revolting to American Medicine—American doctors who have developed a procedure of widely distributed medical care, which is the most effective that has ever been provided for any comparable number of people anywhere at any time. More than 25 million people are now provided with needed protection through the Blue Cross. With the expansion of this physician-sponsored medical service and employer-employee group insurance, other tens of millions can also be furnished the same adequate care with easier payments of the cost.

The medical profession recognizes that war production concentration and the development of new methods has resulted in a woeful neglect of hospital construction and other physical facilities essential to best medical care. The members of the American Medical Association through the formal action of their Board of Trustees endorsed the granting of federal subsidy to eight state and local groups to make thorough surveys of hospitals and other medical surveys and to appraise the needs of the various communities respectively; and to supplement the resources of state and other local groups to be used for providing facilities here needed. Senator Hill of Alabama and Burton of Ohio introduced in the United States Senate, February 14, 1945, bill 191, which makes full provisions for all such needs. The American Medical profession endorses and will adequately support the passage of the Hill-Burton proposals.

The Wagner-Murray-Dingell bills would give to the Federal Agency full control of all labor and working conditions throughout the land. It would give authority to one man to continuously shift workers from area to area and state to state. When making a factual analysis of the Medical and Hospitalization provisions of the Wagner-Murray senate bill 1161, John M. Pratt of the National Physicians Committee for the Extension of Medical Service, comments, "For too long, a semi-complacent medical profession, too proud really to protest, too overworked and over-

(Continued on Page 400)

# Progress in Allergy

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## PEDIATRIC ALLERGY A Critical Review of Recent Literature

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### DEVELOPMENT OF THE ALLERGIC CHILD

To the pediatrician perhaps the most fascinating facet of the study of allergy is the detection of evidence of the allergic state as early in life as possible. This is all the more true since in many instances because of our knowledge of the ascendants or siblings we know in advance which infants are most likely to develop allergic manifestations. Campbell<sup>10</sup>, in the first paper of its kind, has reported with almost telegraphic brevity on the general subject of allergic manifestations of the newborn. His article embodies the results of a questionnaire sent to some six hundred of the leading obstetricians, allergists and pediatricians of North America and his own personal experience.

According to the answers obtained from this questionnaire, the following in the newborn should make one suspicious of potential allergy: Retro-auricular intertrigo; seborrhoea capitis with or without other evidence of seborrhoea; intestinal bleeding after feeding cow's milk; geographical tongue; visible peristaltic waves; intrauterine hiccup; infants with pyloric stenosis who continue to vomit after operation; excessive rubbing of the nose (the so-called "allergic salute"); excessive sneezing, especially if nasal smears show eosinophilia; excessive hunger on a formula which contains sufficient calories; allergic colic which must be differentiated from colic due to swallowed air; excessive reaction to silver nitrate drops; excessive reaction to ammoniated mercury ointment or other salves or oils used to prevent intertrigo; urticaria shortly after breast feeding which usually disappears before the next feeding; intolerance to orange juice and cod liver oil; unusual sensitivity to sugar; early excoriation of the buttocks; asthma especially in a breast-fed baby whose mother's scalp shows excessive dandruff; laryngospasm; glossitis; edema of feet and hands; unstable parentage; hypertrophy of the thymus; and lastly, an infant born of allergic parents.

There are doubtless many items in the above list which pediatricians will challenge. It would have been helpful had Campbell stated what he considered to be the duration of the newborn period. Most pediatricians, even those majoring in pediatric allergy, have not seen in the newborn many of the conditions enumerated above. In my own experience, retro-auricular intertrigo, which was described by Kugelmas<sup>46</sup> as an indication in early infancy of a potentially allergic child, has occurred chiefly as an indication of failure of the mother to cleanse properly behind the ears. When she was instructed as to the proper procedure for so doing, this sign of the potentially allergic child usually disappeared. In the instances in which it persisted it has indicated a tendency to seborrhoeic rather than to atopic dermatitis.

Visible peristaltic waves in the newborn period are so common that they may be considered physiological. However, the general impression is that infants with pyloric stenosis, whether or not they continue to vomit after operation, are potentially allergic children. It is not at all uncommon for infants with pyloric stenosis to vomit

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postoperatively. This has been discussed by Faber and Davis<sup>27</sup> and it does not seem reasonable to consider such vomiting as additional evidence of potential allergy. The newborn infant who has asthma must be considered already an allergic child by virtue of this typical manifestation. The thought that unstable parentage predisposes to allergy in the offspring is interesting but needs further elaboration before it will be accepted by pediatric allergists.

An analysis of the history of 200 of Campbell's allergic children seen in later infancy and childhood showed that 25 per cent revealed allergic symptoms during the newborn period. He also reports very briefly twenty-four cases of allergy of the newborn in his own practice. In all instances, apparent cures resulted following the removal of offending allergens. These cases are particularly interesting:

*Case 1.*—A newborn infant whose older brother died of anaphylactic shock after his first breast feeding, presented similar symptoms when one drop of his mother's milk was placed on his tongue. The infant was promptly weaned. One month later he gave a four plus cutaneous reaction to human breast milk.

*Case 2.*—Another newborn infant on being placed at the breast on the second day of life went into a state of anaphylactic shock so severe that the head nurse felt it advisable to baptize him during the episode. He was resuscitated by means of epinephrine hydrochloride and artificial respiration and the same occurred when he was given one drop of his mother's milk. He too was weaned forthwith and later reacted to human milk on skin testing.

Allergy to human milk is so rare and knowledge of it is so important it is hoped that eventually Campbell will report these cases in great detail.

*Case 3.*—A newborn infant who would develop eczema each time his mother received an inoculation for pollinosis. It is presumed, although Campbell does not say so, that the child was being breast fed at the time.

*Case 4.*—A newborn infant who developed eczema in the hospital which was later shown to be due to starch in the nurse's uniform.

Next to the detection of the potentially allergic infant, the most interesting privilege of the pediatrician is the study of the development of the allergic state as this infant develops. Clein<sup>11</sup> has reported a follow-up study of 100 allergic infants over a period of ten to fifteen years. All of these were observed in private practice. The test for allergy in every instance as the cause of symptoms was the clinical test: i. e., the disappearance of symptoms on removal of the offending allergen. Orange juice was found to be the single most important allergen producing initial allergic sensitization or shock. The "allergic tongue" (geographic tongue) as the first symptom of allergy was noted in three cases. In 98 per cent of the allergic infants the first allergic symptoms, as observed by Clein, were rash (eczema), vomiting (pyloric spasm); gastro-intestinal distress (more or less persistent colic, gas, diarrhea and constipation), asthma, perennial allergic rhinitis, allergic tongue, hay fever, and hives.

Ninety-eight per cent of the allergic infants developed major allergic symptoms in their first ten years. They occurred in this order: perennial allergic rhinitis, pollinosis and asthma. However, Clein observed that the first allergic symptoms have no relationship to the type of major allergy which will develop in later years. Most cases of major allergy developed before the age of six years; only 15 per cent in this series occurred after six years. While prophylactic treatment, which Clein discusses, advocated early and carried out thoroughly, did not prevent the development of major allergic symptoms as the child grew older, nevertheless Clein feels that it probably minimized the course of the disease and its complications.

Parents are frequently told that they should not worry about their children's allergy, since it will disappear as they grow older. Black<sup>6</sup> states that this does happen but is the exception rather than the rule, and that while all of us see persons who have had some form of allergic condition in earlier years which has been eventually lost, yet the number recovering spontaneously is small. In Black's esti-

mate it is not more than 10 per cent, which he rightly feels is too small a percentage to depend upon.

The fact that the incidence of asthma and hay fever is about twice as great in boys as in girls suggests that one of the hereditary factors upon which some cases of asthma and hay fever depend is transmitted as a sex-linked recessive factor. This observation suggested to Mollholm<sup>51</sup> that there might be a relationship between asthma and hay fever in children and red-green color blindness, which is known to be dependent in all instances on a sex-linked recessive factor. One hundred sixty-five asthmatic male patients and 192 hay fever male patients, all thirteen years of age or less at the time of onset of symptoms, were tested for red-green color blindness by means of the Ishihara tests. The incidence of red-green color blindness in the whole group of patients was 8.4 per cent, which was about twice as great as the incidence of about 4 per cent in unselected males. This difference is statistically highly significant. The relationship thus found between red-green color blindness in men and some cases of asthma and hay fever in boys probably depends in part on a sex-linked recessive factor.

## GENERAL CONSIDERATIONS

Pratt<sup>54</sup> briefly discussed the American approach to allergy in childhood and briefly reviewed the clinical method. He states that the chief difference between the United States and Great Britain is that in this country the immunological method of approach is particularly emphasized, whereas in Great Britain the therapeutic is more in favor.

Holt<sup>41</sup> warns that while skin tests are often of the greatest aid in the solution of an allergic problem, they must not be interpreted too literally. Before one can conclude that a positive reaction is clinically significant it must be confirmed by a clinical test. Holt points out the fact, which he states has received but scant attention in books on allergy, that summation of effects may occur when two allergens, neither of which produces much reaction alone, are encountered together.

Dighiero<sup>21</sup> has reported from Uruguay on 170 allergic infants. There were ninety cases of asthma, thirty of asthmatic bronchitis, seventeen of eczema and eleven of urticaria. The remainder were of various other conditions. Thirty-five per cent of the patients reacted to foods; 20 per cent reacted to both foods and inhalants; 15 per cent to inhalants exclusive of pollens; 2 per cent to pollens alone, and in 28 per cent of cases the allergen was not found on skin testing.

The perennial problem about what to do in the case of the allergic child who wishes to go to camp in the summer has been discussed by Glaser.<sup>7</sup> Because of the emergencies to which an allergic child is particularly susceptible, the primary consideration for such a camp is a resident physician, or at least a resident nurse with a physician readily available upon very short notice. Children on highly restricted diets should not be sent to camp even on diets which require the elimination of particular foods which may easily be omitted unless the child is known to be very co-operative. It is particularly important that the allergic child be immunized against tetanus by means of tetanus toxoid. The attention of the camp physician should be called to this fact so that the child if injured will not needlessly be given tetanus antitoxin. If for some reason the child is not actively immunized against tetanus the camp physician should be instructed not to use horse antitoxin but bovine antitoxin except in those children known to be sensitive to beef or milk, in which case a despeciated antitoxin should be used. If the child suffers from pollinosis it is advisable to send him to a pollen-free area if possible. The child should remain there until the pollen season is well over, even though this may require omitting the first week or two of school. All injection treatments which are given at home should be given in camp also but careful directions should be given the camp physician so that they will be properly administered.

The child should take to camp an adequate supply of the medications he customarily uses for his allergic difficulties. These should be clearly labeled so that the camp doctor will know exactly what is being used. The child should also take with him his own bedding, special pillows, blankets or blanket covers, a mattress or mattress cover if necessary. Unless he rooms by himself it will also be necessary to loan similar equipment to his roommate.

If the child is doing well, the effect of swimming upon his allergic condition is a problem to be judged in every individual case. Children with chronic atopic dermatitis may swim. The lesion should be protected with vaseline or some bland ointment. Children with eczematous skins are often quite sensitive to light and care should be taken to avoid sunburn. A coat of tan should be acquired very gradually. If tar ointments are used the skin is particularly sensitized to light and either special care must be used or an ointment not containing tar should be substituted.

In general, the child should avoid animals in camp as well as at home. In crafts and hobbies taught at camp he should avoid the preparing and mounting of animals with fur or feathers. It is better to interest the child in mineralogy or geology or the study of fossils or fish. He should not go on over-night hikes where he might have to sleep on the ground or in a barn. He should be taught to avoid poison ivy and should he be sensitive to this, prophylactic measures should be instituted before he goes to camp. Abnormally severe reactions to an insect sting may occur and if this happens the nature of the insect should be determined so that specific prophylactic therapy may be given if necessary.

## ALTITUDE AND CLIMATE

It is a common belief that high altitudes favorably influence allergic diseases. The fact that this is not true is gradually being taught to us by our neighbors who practice in the great republic to the south. Mallén<sup>48</sup> has given a most enlightening discussion of the subject of allergy, including its relationship to altitude, in Mexico. Baker<sup>2</sup> has reported in even greater detail with particular reference to children. She states that evidence has been accumulated in Mexico City (altitude 7,325 feet) which indicates that allergic reactions are more common there than at lower altitudes. From this the author has deduced that (1) mountain sickness, the symptoms of which are the same as those of allergic reactions, may be explained on an allergic basis, and (2) the higher the altitude, the more allergy will be encountered. The symptoms of mountain sickness to which Baker refers as being similar to those of allergy, are nausea, vomiting, depression both mental and physical, and diarrhea. Baker states that her points are supported by case histories on 500 cases fifteen years of age or under. The cases were almost equally distributed as to sex and comprised 350 American or European and 150 Mexican patients.

Of the 500 individuals, 167 had either hives or urticaria, there being twenty-five cases of the latter. Of the 500 cases, 100 had diarrhea with accompanying vomiting in forty-eight cases. The most common offenders were eggs, milk, orange juice, and chocolate in the order named. The symptoms in most instances became acute within three weeks of arrival in Mexico City and cleared up on removing the offending foods from the diet. These reactions are definitely not due to some specific abnormality in Mexico City, as many children develop hives, diarrhea and vomiting from food products imported from the United States such as cod liver oil, canned beef, and evaporated or powdered milk. They clear up when a particular food is omitted from the diet or when the patient goes to a lower altitude where these foods may be taken. The author cites many cases illustrating this last point.

As an explanation for this fact it occurred to Baker that the anoxia experi-

enced in an altitude such as Mexico City may result in a greater absorption and accumulation of protein products than at lower levels. Low pressure is definitely the basic cause of mountain sickness and this definitely modifies various physiological functions. Baker states that she has been able to find only one reference in the literature available indicating an influence of altitude on allergic manifestations. This is the paper by Kopaczewski and Marczewski<sup>43</sup> on anaphylactic shock recording the induction of convulsions in guinea pigs sensitized to beef serum albumen one month previously. These animals together with normal controls were placed in a pneumatic caisson and the atmosphere depressed at a rate corresponding to a rise in the air of 1000 meters per minute until the equivalent of 10,000 meters was reached. At the latter figure all sensitized animals were in convulsions (with the exception of those which had gone into convulsions earlier) and a slow descent was made. At 6,000 meters (in three minutes) all the animals recovered, the only symptoms persisting being a lower temperature. Controls remained normal except for slight lowering of temperature.

Loss of weight characteristically accompanies the anoxia of high altitudes and the reasons for this have been assumed to be loss of appetite, restlessness, diarrhea, et cetera. In those coming to Mexico City a period of about two weeks is usually required in older children for the effect to accumulate and become manifest in symptoms. It is suggested that anoxia occurring at this altitude may result in a greater permeability of the gastro-intestinal tract to offending substances. Baker's recommendations are as follows:

Children with allergic reactions to food do well at this altitude if the following precautions are taken: (1) Avoid overloading on any one food; (2) not giving any one food more than once or twice a week; (3) avoid eggs, chocolate, too much cow's milk, wheat and orange juice; and (4) supplementing the diets with vitamins *A*, *D*, *B* complex, *C*, and calcium. Particular foods discovered to cause trouble must be at least temporarily omitted from the diet.

In Tel-Aviv, Palestine, Feiga and Rosenbaum<sup>2</sup>, according to Unger<sup>73</sup> made meteorologic studies on three isolated dates when many children with chronic asthma developed severe attacks. There were no special changes in weather conditions on these three dates, although the authors point out the asthma may have been due to the sudden appearance of pollens in the air.

## GASTRO-INTESTINAL ALLERGY

Abdominal pain due to food allergy has been discussed by Ratner<sup>57</sup> with his customary thoroughness and clarity. The fact that abdominal pain of allergic origin may be present without confirmatory evidence of a positive skin test may be explained by the fact that the gastro-intestinal tract is sensitized before the skin. He placed abdominal pain of allergic origin in three main categories: (1) Abdominal pain as a minor symptom, (2) recurrent abdominal pain, (3) severe abdominal pain simulating an allergic surgical condition of the abdomen. In the last category mentioned, Ratner pointed out that while the allergic reaction *per se* is reversible, yet the edema may pave the way for bacterial invasion and infection resulting in changes which are not reversible and which indicate surgical intervention. The importance of the therapeutic tests by the oral ingestion of ephedrine or atropin or the injection of adrenalin to relieve symptoms and clarify the diagnosis is mentioned. The reviewer, however, would like to point out that the failure of such a therapeutic test by no means rules out allergy. In this connection one need mention only how frequently adrenalin fails to relieve angio-neurotic edema.

Ratner stated that the most concrete evidence of muscle spasm which may cause the abdominal pain is provided by the x-ray. The allergic abdominal pains may be initiated by (a) spasm of the gastro-intestinal smooth muscle, (b) wheal forma-

tion in the gastro-intestinal wall, (c) spasm of the small vessels of the gastro-intestinal wall, or (d) a combination of these factors. -

In treatment the author referred to his so-called "allergenically denatured diet" for all patients with food allergies. This is based on his belief that heated albumen fractions are coagulated and therefore cannot act as allergens. However, some of the most interesting cases of allergic disorders in infants and children in the reviewer's practice have occurred with specific foods listed in this diet.

Brodrigg<sup>9</sup> has reported a case of vomiting of allergic origin in an infant. The boy was a second child. He had an older sister who had no evidence of allergy, and there was no evidence of allergy in the parents. However, allergy was present in the families of all four grandparents. The mother drank milk liberally before and after the children were born. The patient reported upon was breast fed until he was five months of age. No cow's milk of any kind had been given previous to then. Starting at five months he was occasionally given a few teaspoons of diluted cow milk which had just been brought to a boil and cooled. This was invariably vomited except on the first two or three occasions when small quantities were taken. Further attempts were made with diluted or citrated milk at intervals of a few weeks and the vomiting became more severe. The child, however, had no eczema or other signs of allergy. He still vomited severely at eight months whenever cow's milk was tried and it was then noted that erythema developed on his neck, where it was moistened with the cow's milk. Patch tests with "humanized milk" (cow's milk dried at a temperature below 145° F.) on the infant's arm gave an intense erythema and urticarial wheal about  $\frac{3}{4}$  inch in diameter in twenty minutes. A similar test with undiluted cow's milk after one hour gave a positive but less marked reaction.

The boy was then given a prepared milk called "Almata" which contains casein, egg yolk, and wheat flour proteins but no lactalbumin or lactoglobulin except perhaps minute traces. He did well on this, vomiting only occasionally and slightly and other foods were rapidly added and by nine and one half months he was weaned completely from the breast. On patch testing he did not react to Almata powder, pure casein, and pure lactalbumin (presumably but not definitely known to be of bovine origin). Patch tests with whey were slightly positive and with Seewa powder (whey dried below 145° F.) were positive but less positive than with humanized dried milk. Between nine and eleven months the positive patch tests to humanized dried milk became weaker and disappeared. Specific desensitization was carried out between ten and eleven months of age by the feeding of gradually increased amounts of whole milk. The author believes that the allergen responsible was lactalbumin or lactoglobulin, but since the source of the pure lactalbumin with which the child was tested was not certain, and since lactalbumin and lactoglobulin always occur together, it is difficult to say whether the specific desensitization by mouth was completely successful. With this the reviewer cannot agree as the author's report shows that the infant was well on his way to recovery as evidenced by the rapid decrease in the reaction to patch tests with humanized dried milk, even before oral desensitization was started.

A simple method for oral desensitization to food allergies is greatly to be desired. Urbach<sup>74</sup> has brought forward his propeptans as a means for doing this. Propeptans are derived from individual proteins by digestion with hydrochloric acid, pepsin and trypsin. They contain chiefly proteoses, but also peptones, simple peptides and amino-acids. A guinea pig highly allergized to egg white can be protected against usually lethal anaphylactic shock by a preliminary injection or feeding of egg propeptans. Other propeptans are totally inefficacious. In practice the specific propeptan is given on an empty stomach forty-five minutes before the next meal. In cases of extreme sensitivity, the patient may react to the propeptan itself and for this reason in such cases the patient should test the effect of the inges-

tion of one-tenth of the contents of the propeptan capsule. The specific propeptan must be given for each food to which the patient is allergic. If the symptoms persist and a nutritive allergy is still suspected, then carbohydrates, salt, and acid must be progressively eliminated from the diet. The average period of treatment with propeptans is between two and three weeks. The author refers to the case of a sixteen-months-old boy with asthma due to the ingestion of milk successfully treated with propeptan therapy.

The reviewer's experience with propeptans has been small but not satisfactory. It is unfortunate that this method has not had a more extensive trial by other investigators. Urbach's thorough work in this field and the importance of confirming or disaffirming his conclusions is so great that it is much to be regretted that others who have worked in this field have not published the results of their investigations, either affirmatively or negatively.<sup>23</sup>

## ALLERGIC DERMATITIS

Two excellent reviews have appeared on the subject of eczema. These reviews do not overlap appreciably probably because the review of Epstein<sup>25</sup> is written from the viewpoint of the dermatologist and that of Rackemann<sup>55</sup> from the viewpoint of the internist and both from that of the allergist. Epstein's discussion of nomenclature is particularly interesting and his suggestion of the term "epidermitis" to replace the term "contact type dermatitis" merits careful consideration.

Generally speaking, allergists have paid little or no attention to the histopathology of the skin lesions with which they have dealt, and particularly is this true of the eczematoid dermatoses. It is for this reason that the presentation of this subject by Miller<sup>60</sup> at the first annual meeting of the American College of Allergists in June, 1944, was one of the highlights of the instructional courses given at that time. Miller stated that contact dermatitis differs from the other diseases by the type of vesicle, little or no acanthosis, and a mild superficial inflammatory reaction. Neurodermatitis (chronic atopic dermatitis) has a non-edematous regular acanthosis, thickening of the walls of the small arteries and a focal cellular reaction. Nummular eczema has the epidermis and cutis of neurodermatitis plus an intra-epidermic vesicle. Eczema is not a disease *sui generis* but is probably an expression of several diseases having similar findings. It differs (and here he refers to what pediatricians call acute atopic dermatitis) from the other three forms of eczematoid dermatitis (contact dermatitis, chronic atopic dermatitis, and nummular eczema) by an extensive cutis (corium) reaction involving the capillaries and an intense diffuse cellular reaction. There is also an irregular acanthosis most often with all signs of edema but sometimes with little or none. In all four groups of the disease the pathological process is superficial. In none of these is degeneration found and the cellular reaction never contains plasma, epithelioid or giant cells. There is no evidence of sequelae once the process subsides. In contact dermatitis, the epidermis plays a prominent role; in neurodermatitis the small arteries; in nummular eczema, the same as neurodermatitis plus a peculiar epidermic vesicle; in eczema, the cutis (corium) is the important feature, especially the involvement of the capillaries. This article, which fills a long-felt need by pediatric allergists, is beautifully illustrated and has to be read to be appreciated.

Cooke<sup>13</sup> has contributed a thought-provoking discussion of the subject of atopic dermatitis. He states: (1) "The term 'atopic dermatitis' is unfortunate in that it is used by some to indicate the hereditary feature as the word originally meant; by others to indicate the existence of an etiological significance of the wheal-reacting type of allergy and by many interchangeably as though the two were synonymous." (2) "The term 'atopic dermatitis' is inappropriate as it has come to imply that skin testing for immediate wheal reactions is a diagnostic procedure in eczema of the infantile type, which . . . it is not." (3) "Intradermal or scratch

tests must be discarded as diagnostic procedures in eczema, and the terms atopic dermatitis and neurodermatitis should be eliminated from our nomenclature." However, Cooke does not suggest an appropriate substitute term for "atopic dermatitis."

Most pediatricians agree with Hill<sup>38</sup> to the effect that "the term atopic dermatitis represents a useful and accurately descriptive nomenclature to apply to a well-defined clinical and immunological condition which is as much a distinct entity as diabetes is." Epstein<sup>25</sup> states: "The term 'atopic dermatitis' is a valuable addition because it is the only unmistakable term for this form of eczema. For this reason, it should be used, regardless whether one agrees with Coca's concept of atopy or not."

The old term, "infantile eczema," is too all-inclusive and too confusing. The term "atopic dermatitis" now connotes to the pediatrician a specific disease of infancy or its chronic form as it occurs in late infancy, and throughout the rest of childhood and sometimes almost the rest of life. To classify, for example, the most common form of contact dermatitis in infancy, the ammoniacal dermatitis of the diaper area and atopic dermatitis of the face in infancy, both under the term of "infantile eczema" is a step backwards. I would however agree to the elimination of the term "neurodermatitis" because this condition is now clearly recognized as a chronic form of atopic dermatitis and should be so designated. If this term is retained, it should apply only to such forms of this dermatitis as can be definitely shown not to be of allergic origin.<sup>25</sup>

As regards Cooke's second statement that intradermal and scratch tests must be discarded as diagnostic procedures in what most pediatricians now call "atopic eczema" is to highlight what most pediatric allergists realize, i. e., that the skin tests are related to the whole study of the patient in the same manner that the electrocardiogram is related to the complete study of the patient with heart disease, or blood sugar determination is related to the complete study of the patient with diabetes. Both the electrocardiogram in the case of the patient with the heart disease and the blood sugar determination in the case of the patient with diabetes may be left out of the study and the physician can still do well in diagnosing and treating the condition; he can do much better if he is privileged to do all the indicated laboratory procedures and in atopic dermatitis skin testing is just one of these procedures.

Cooke's point that a skin test in order to be diagnostic of the type of dermatitis must reproduce the type of dermatitis studied, is well taken. However, it can be reconciled with the wheal type of reaction induced in testing for atopic dermatitis. The most common reaction illustrating this which repeatedly occurs in skin testing in early infancy, is the skin test for egg white. The great majority of infants with atopic dermatitis react to egg white on scratch testing by the production of a wheal. These infants in most instances are also clinically sensitive to egg white. The type of reaction induced by skin testing is dependent both upon the degree of the sensitivity of the skin and the concentration of allergen brought into contact with the test site. If the skin is fairly sensitive and relatively enormous concentrations of allergen are brought into contact with the test site as occurs in ordinary scratch or intradermal tests, the reaction is overwhelming and is a wheal response; if the same sensitive infant is subjected to a clinical test in which he is fed a drop of egg yolk, the egg white proteins contained in and diluted by the lipoids of the yolk are further diluted by the tissue fluids and a minute amount of the egg white is brought by the blood into contact with the sensitive skin over a relatively long period of time as compared with the acute experiment of the dermal test and the more chronic form of reaction, the eczematous or atopic type of dermatitis appears in the infant's skin. Cooke's postulates are fulfilled in both instances because if the same child is fed a large amount of egg white, he does not break out with eczema but with hives; the acute experiment with the dermal test

is thus reproduced from within. Every pediatrician sees this happen repeatedly in his practice; in recent years not so often, since it is no longer a common practice, as formerly, to introduce egg yolk into the diet at the early age of three months. What has been described happens occasionally with other foods but less often and less dramatically than with egg.

The dermal test also has the use not commonly emphasized in assisting in the addition of foods to the diet of the allergic infant. If skin tests are done with a series of foods which one is considering adding to the infant's diet, it is not the part of wisdom to give those foods which react positively. One's chances of success are much greater if the negatively reacting foods are used. Probably the most common example of this is when cereal is to be added. Our cereal grains are biogenetically closely related, all being modified grass seeds. If one tests with wheat, rye, rice, oat and barley and obtains positive reactions to all but rice for example, it is only sensible to add rice as the infant's first cereal.

Strickler, Herman and Grumach-Fabian<sup>68</sup> studied gastric secretion in infantile eczema. The children varied in age from nine months to twelve years and comprised thirty-five patients with atopic dermatitis, four with seborrhoeic eczema, two with the ichthyotic variety and nine controls. The Ewald test meal was used. Free hydrochloric acid in the eczema group averaged 24.8 units and total acid 49.6 units. In the control group the free hydrochloric acid was 23.8 units and the total 43.3 units. The authors concluded that the values for infants with eczema failed to show any pronounced or consistent variation, either in free or total hydrochloric acid.

Physicians still continue to question the advisability of hospitalization of the eczematous child.<sup>29</sup> This question will always be in order but the situation as it stands at present has been thoroughly discussed in an original article by Epstein.<sup>26</sup> His contribution is significant not only because of the importance of the subject but because it is the first on this subject written by a dermatologist and also the first since the sulfonamide era began. He reports a series of 100 consecutive hospitalized cases of infantile eczema up to two years of age without deaths. The cases were classified as follows: atopic dermatitis, seborrhoeic dermatitis, contact dermatitis, and infectious eczema, chiefly intertrigo.

Sixty-four of the infants were admitted with uncomplicated eczema. Of these, fifteen or 23.4 per cent developed complications. However, all the complications but one occurred in infants with atopic dermatitis. The author believes that these occur chiefly as acute exacerbations of subclinical respiratory or gastro-intestinal allergy, and also that the susceptibility of the infant with atopic dermatitis to complications indicates a fundamental difference between this infant and the infant with the other types of eczematoid dermatoses.

Kaposi's varicelliform eruption (to be discussed subsequently) occurred as an admission complication in three cases. All survived. One patient developed a paralysis of one foot which was considered by the attending pediatrician to be possible evidence of poliomyelitis. Epstein felt, however, that in view of the fact that the virus of herpes simplex is a neurotrophic virus, the possibility exists that the paralysis might have been a consequence of that infection.

A much higher degree of eosinophilia is noted in atopic dermatitis as compared with nonatopic dermatitis. The average eosinophilia is 9.7 per cent which is just about twice as high as in the nonatopic dermatitis and about ten times as high as in other skin diseases used as controls. Anemia, however, was found just as often in the eczematoid dermatoses as in the other dermatoses of children.

The mortality of zero in the author's series is explained chiefly by the use of sulfonamides when indicated and by excellent nursing care. The author felt that since the advent of sulfonamides, death from eczema appears to have become an avoidable complication.



A valuable part of this paper is Epstein's discussion of sudden death in eczematous infants without apparent cause and the review of the constructive contribution by Davies<sup>16</sup>, as well as the other literature relating to this subject. Epstein is inclined to favor the theory of Sulzburger<sup>69</sup> that phenol poisoning from tar in combination with interference with cutaneous respiration and the instability of the autonomic nervous system would explain satisfactorily the symptoms as well as the other circumstances of some of the acute deaths from eczema.

Despite the repeated warnings which have been issued regarding exposing an eczematous infant to a sibling or some other individual with a fresh vaccination, deaths from vaccinia in eczematous infants continue to occur. Such a case is reported in detail by Petersilge and Toomey.<sup>52</sup> This occurred in an eight-month-old white infant who had been eczematous since birth. A six-and-a-half-year-old sister had been vaccinated nine days before lesions appeared on the patient. There was a question as to whether the sister's lesions were dried with a wash cloth later used on the baby with eczema. Five days after the appearance of lesions on the skin, the baby was hospitalized with a generalized vaccinia. The white blood count was 13,500 with 39 per cent neutrophils and 17 per cent eosinophils. The Paul test was positive. The infant was treated with gentian violet, sulfadiazene, and human convalescent scarlet fever serum. However, she developed pneumonia and died fourteen days after the rash had appeared. Culture of the heart's blood showed a non-hemolytic streptococcus. Complete autopsy was done, and this showed patchy atelectasis, ulcerative laryngitis, ulcerative stomatitis, acute hyperplasia of the spleen, and generalized lymphadenopathy. There was moderate anemia. The kidneys, brain and spinal cord were completely negative.

Hershey and Smith<sup>37</sup> stated that generalized vaccinia in persons with eczema has been called "eczema vaccinatum." The incidence is reported as a complication of vaccination in about one in twenty thousand cases to one in ninety-six thousand and the case fatality rate is about twelve to thirty per cent. About two-thirds of the persons in whom this complication occurs have diseases of the skin and many are children with eczema. The incidence of eczema vaccinatum, however, must be much greater than is indicated by these figures as many cases occur which are mild and which are not reported and this probably happens even when some cases are severe. For example, in my own practice I have seen at least six of these and only two were severe enough to require hospitalization. None of these cases were reported in the literature. Many others have doubtless had the same experience.

The authors report a case of eczema vaccinatum in a twelve-month-old girl with an exacerbation of eczema. Her brother had been vaccinated twelve days before admission. The rash appeared ten days after admission to the hospital and three days after the development of the fever. The clinical diagnosis of generalized vaccinia was supported by the recovery of vaccine virus through animal inoculation and through demonstration of protective antibodies against vaccine virus in the patient's blood.

In conclusion, Hershey and Smith state that agents closely resembling the herpes simplex virus have recently been recovered from similar eruptions known as Kaposi's varicelliform eruption or pustulosis varioliformis acuta. These eruptions also occurred in patients with eczema and were formerly considered identical with eczema vaccinatum. A considerable number of patients have failed to yield either vaccinia or herpes virus, despite appropriate tests. This fact may be due to the localization of yet other viruses (as possibly chickenpox) in the areas of injured skin offered by these patients.

Interest in what is known as Kaposi's varicelliform eruption has been very great in the past couple of years. Barton and Brunsting<sup>4</sup>, have provided a thorough review of the literature on the subject. They reported that atopic dermatitis was present in 80 per cent of the cases and 75 per cent of the cases were children under four

years of age. The mortality rate was 25 per cent, being much higher in children than in adults. A subsequent detailed discussion of this subject by Wenner<sup>77</sup> calling attention to the fact that this disease is probably in most instances a complication of eczema with the virus of herpes simplex was discussed in the first of these reviews.<sup>32</sup> Lynch<sup>47</sup> reported one case of varicelliform eruption in an infant two-and-a-half years of age who had a mild atopic dermatitis in the cubital areas. Three days before the onset of the child's illness the father suffered from herpes simplex of an eyelid accompanied by herpetic conjunctivitis. Another case occurred in a ten-month-old boy with a fairly generalized eczematous eruption of eight months' duration. The mother had herpes labialis simplex for two days before the eruption occurred. He also reported two cases in adults with eczema, one of whom had had herpes labialis two days before the onset and in the other there was no known history of exposure to herpes or vaccinia. In all four cases the presence of the herpetic virus was demonstrated. The author points out that the eruption originally termed "eczema herpetiforme" by Kaposi because it resembles herpes simplex actually is herpes simplex in an extensive form. Hence this disease should be called "eczema herpeticum" or spoken of as extensive herpes simplex complicating eczema (or other dermatosis).

The emphasis on Kaposi's varicelliform eruption (eczema herpeticum) in recent years has tended to overshadow the fact that eczema may be complicated by infections which are not of virus origin. In this connection the communication of Boisveit and Powers<sup>7</sup> is of significant interest. These authors point out that atopic dermatitis and streptococcal fever (rhinopharyngitis, cervical adenoiditis, low grade fever of several weeks' duration) are common diseases in the same period of life, the first three years.

In thirty-nine cases of secondarily infected eczema, hemolytic streptococci were recovered from twenty-six (66 per cent). From this small series it would appear that hemolytic streptococci are associated with infected eczema in about two-thirds of the cases. In four of the seventy-six cases of eczema admitted to the hospital there was present a lesion which went through the stages of papule, vesicle, pustule and crust and from these a herpes simplex-like virus was demonstrated by Wenner.<sup>77</sup> Of thirty-six clinically infected hospital patients whose skin cultures showed hemolytic streptococci, twenty-nine (77 per cent) also carried that organism in their rhinopharynx. Blood cultures were positive for hemolytic streptococci in three of the thirty-six infants with clinically infected eczema with skin cultures positive for that organism. It would appear that eczema in a child who has streptococcal fever or who is a carrier of hemolytic streptococci is likely to become infected.

Clinical differentiation between infected and noninfected eczema is not clear cut. Weeping is perhaps the most important single differential characteristic suggesting that an eczema is infected. Adenopathy, commonly present in eczema, is more marked when infection is present. Regardless of infection, a leukocytosis and an eosinophilia are often present in patients with eczema and are of little differential assistance.

For treating the hemolytic streptococcal infections the author used sulfonamides both orally and locally and concluded that there appears to be no support in clinical experience for oral administration of sulfonamides in these conditions. A skin level of approximately only one-half of that of the blood is obtained. A much higher concentration of the drug can be obtained locally by topical application. Five per cent sulfathiazole in white vaseline was found to be the most satisfactory preparation for local use. The authors observed that the healing of the infection was ameliorative but not curative of the eczema, and the infection, though not chronic, tends to recur because it is usually a part of streptococcal fever, a sub-chronic ailment.

Since the sulfonamide ointments were used generally for more than five days, the question of causing possible sensitization to sulfonamides was considered. At present the decision rests with the attending physician as to whether this risk is worth while. Holt<sup>41</sup> prefers sulfadiazene to sulfathiazole for local application because sensitization to sulfathiazole occurs much more easily. Boisvert and Powers<sup>7</sup> observe that it is possible that sulfonamide treatment of infected infantile eczema may be replaced by other local medication, as penicillin. In this connection I should like to suggest that tyrothricin should receive more consideration for use in topical application. Its bacterial spectrum is, even broader than that of penicillin. Since it is not injectable it would appear preferable to use tyrothricin locally, reserving penicillin for those patients who require an antibiotic by injection. Although sensitization to penicillin apparently does not occur often, it does occur, and if tyrothricin will serve the purpose locally as well as penicillin it should be used for that purpose, thus sparing the patient the possibility of sensitization to penicillin in a condition which may be adequately treated by some other antibiotic.

A study of the clinical evaluation of soy bean food in the eczema of children has been made by Stoesser.<sup>66</sup> In this study, adequate environmental control and local treatment were instituted. Diet was started, apparently not on the basis of individual skin tests but as a type of elimination diet. A total of thirty-seven cases was studied. Twenty-nine patients accepted the soybean well. Undesirable looseness and frequency of the stools occurred in fourteen cases but was helped by the addition of a kaolin and pectate mixture. Of the twenty-nine cases who took the soybean milk well, the eczema disappeared in eighteen and was much improved in eleven. Twelve of the infants were found sensitive to milk. Of these, only five gave positive cutaneous tests to cow's milk protein. The remaining seventeen were considered to be sensitive to more than one food. However, after weeks of soybean food ingestion, they were able to tolerate better the other foods to which they had previously given clinical evidence of sensitivity.

A discussion on the nutritive value of soy beans has been published by Barnes and Maack.<sup>3</sup> This contains a detailed review of the literature but unfortunately omits reference to the work of Ruhrah<sup>60,61</sup> and of Hill and Stuart<sup>39</sup>, so important to the pediatric allergist.

According to Holt<sup>41</sup>, dehydrating procedures are unquestionably of value in treating infantile eczema. Restriction of the water intake is not advisable, but a marked improvement often follows the elimination of supplementary carbohydrate food. Top-milk formulas such as were popular in infant feeding some years ago are often helpful. Such high-fat formulas cause elimination of water from the body and loss of weight. Overfeeding is always to be avoided. The administration of potassium salts, a measure recommended a few years ago, is of little value unless accompanied by restriction of sodium chloride and at best makes but a slight contribution.

## CONTACT TYPE DERMATITIS (EPIDERMITIS)

Plotz<sup>53</sup> has reported two cases of contact dermatitis in children ten months and six months of age respectively, due to hair lacquer used by the mothers. The ten-month-old child had been treated for "eczema" of the face for eight months without success. The dermatitis involved the forearms, especially the inner sides, right side of the cheeks and part of the forehead. No unexposed portions of the body were involved. The lesions in the six-month-old child involved the forearms, one cheek, most of the forehead and temples and the back of the neck. In both instances, patch tests with the mother's hair lacquer were strongly positive and the eruption disappeared when the mother discontinued this form of hair dressing.

## SINUSITIS

Birdsall<sup>5</sup> in his paper on the diagnosis and treatment of sinusitis in children has some most interesting remarks relating to mouth breathing. He stated that when true mouth breathing occurs, it is almost always a sign of sinusitis or of two other very rare conditions, congenital atresia of the posterior choane or nasopharyngeal tumor. The author distinguished between "mouth-breathing" and "mouth-openness" and stated that a very instructive experience may be easily enjoyed by visiting a children's ward at night. The proportion of children who are found sleeping with open mouths can be found to correspond very closely to the proportion whose age is below six years, the age at which the mandible begins to grow rapidly to accommodate the permanent teeth.

The "mouth-openness" of small children, misnamed "mouth-breathing," is commonly spontaneously cured by increase in the length of the body of the mandible. The angle of the mandible, which is  $175^{\circ}$  at birth, is reduced to  $110^{\circ}$  after puberty. Whether the patient is breathing through the nose or through the mouth may be easily determined if the observer will quietly approach with a cold spatula and hold it beneath the nostrils. The author makes this statement with which I believe no American pediatrician will agree: "I believe allergic nasal conditions to be very rare in children. I have very few notes of this occurrence in children and do not recall having recorded it except in hay fever." Birdsall states, in discussing the same subject, that the typical tissue response to the streptococcus, is the production of edema, not pus. Tonsillar inflammation is usually a result of sinusitis, as also are otitis media, conjunctivitis, and many types of deviation from normal behavior. The important result of inflammation of the nasal and sinus mucous membrane is a mechanical difficulty occasioned at the ostia by the swelling of the membrane in an inexpandable bony ring, which leads to a "sinus-block." The indication is to reduce edema of the ostia so as to permit nasal entry of air into the sinuses, and to facilitate the escape of the increased secretions. For this purpose he recommends the use of vasoconstrictors, especially neosynephrine one-quarter per cent, or ephedrine hydrochloride one-half per cent, in normal saline in Proetz displacement therapy.

McMahon<sup>49</sup> stated that the removal of tonsils and adenoids will cure 80 per cent of sinus infections in children. Polypi, deviated septi, and high-arched palates are predisposing causes in the remaining cases, with allergy and constitutional conditions as contributing factors. Extensive surgery in children is unwarranted except in emergencies such as exenteration of an infected sphenoid or ethmoid sinus because of co-existent optic neuritis. Chemotherapy has a definite place in the treatment of sinusitis. Local methods of treatment are detailed, particularly nasal irrigations.

## ASTHMA

Invariably every parent of a child who has repeated attacks of bronchial asthma asks the question, "Doctor, will this damage my child's heart?" The answer to this, based on clinical experience, has been that the child will undoubtedly suffer no harm even though he may have repeated attacks of severe bronchial asthma. However, it remained for Derbes and Engelhardt<sup>19</sup> to subject this question to scientific investigation. Roentgen ray and electrocardiographic studies were made. A study of the heart size and contour of twelve asthmatic children ranging in age from five to fourteen years whose asthma varied in duration from one to nine years disclosed no abnormality fluoroscopically or on roentgenograms. They also studied<sup>23</sup> a series of seventeen children with an average age of 9.3 years; the youngest being five and the oldest fourteen years. The average duration of the asthma was 4.7 years with a minimum duration of fourteen months and a maximum of nine years. Detailed studies of the electrocardiograms were reported as normal. The authors felt that uncomplicated bronchial asthma in childhood is not a factor in heart disease. They state that this does not militate against the production of heart dis-

ease subsequent to pulmonary fibrosis, emphysema, bronchiectasis and other pulmonary complications seen in the chronic asthmatic state.

Mothers of asthmatic children who are thin and underweight frequently ask about the possibility of pulmonary tuberculosis in the asthmatic child. Black<sup>6</sup> said that he has seen few adults and no children in whom tuberculosis and asthma were co-existent. As far as children are concerned, the reviewer's experience confirms Black's observation.

Taylor<sup>71</sup> attempts to make a differential diagnosis between what is called "chronic pulmonary catarrh," a term introduced by Leys in 1927, and true allergic asthma. Of sixty-three patients under the age of fourteen years observed in the asthma clinic at the General Hospital in Birmingham, twelve had true allergic asthma. His criteria for true allergic asthma are: previous occurrence of infantile eczema, direct relationship between the attacks and exposure to foreign proteins, freedom from respiratory symptoms and signs between attacks, greater frequency in summer months, normal lungs physically and radiologically and response to adrenalin or ephedrine. The remaining fifty-one cases were examples of chronic pulmonary catarrh, their first diagnosis being variously asthma, recurrent bronchitis, or recurrent coughs and colds, et cetera. In a further group of thirty-eight children also under fourteen years of age seen in private practice, thirty-three showed evidence of recurrent catarrhal infections of the respiratory passages, only five being cases of true bronchial asthma.

The author stated that of the entire group of 101 children studied, 84 had associated underlying respiratory infections. Recurrent colds or upper respiratory catarrhs were followed by generalized pulmonary symptoms, as coughing, tight chest, wheeziness and more or less "asthma." In other cases persistence of cough was the most troublesome complaint. Most of the children seemed to show an increased susceptibility to respiratory infections or else had a chronic infection which was lighted up by unduly trivial circumstances such as changes in weather, exposure to cold winds, dampness, fog, rain, and all the attacks were more frequent during the winter and spring months. Taylor stated that Leys showed how the term "chronic pulmonary catarrh" usefully describes this common condition which numerous authorities have diagnosed under the terms fibrosis of the lungs, fibroid lungs, recurrent bronchitis, unresolved pneumonia, interstitial pneumonia, chronic bronchial pneumonia, peribronchitis, et cetera. Few necropsies have been recorded. Taylor stated that the differential diagnosis has to be made from true allergic asthma and from bronchiectasis and tuberculosis, both of which in the past have been commonly mistaken for chronic pulmonary catarrh. Treatment for chronic pulmonary catarrh is most satisfactory by climatic measures but breathing exercises are of value and will relieve the majority of cases.

It appears to me that what the author describes under the term chronic pulmonary catarrh embraces probably in most instances what we term "asthmatic bronchitis." However, the term doubtless includes a group of chronic pulmonary diseases not truly bronchial asthma. It is unfortunate that a study of the eosinophils in the nasal and bronchial secretions was not made in his cases. The presence of eosinophilia in such secretions places the burden of proof on the investigator who states that these conditions are not truly allergic in origin.

Dust bronchitis is a condition which may possibly be confused with persistent cough of allergic origin and possibly with bronchial asthma. Toomey and Peter-silge<sup>72</sup> described an outbreak of noninfectious bronchitis occurring in an orphanage in Cleveland when the children played on a large field during fairly dry weather. During this time the surface of the field was covered with finely pulverized dust and the symptoms apparently arose from the inhalation of this material. This type of bronchitis has been previously noted in the Dust Bowl area. The average duration of the illness in each case was about two weeks. The principal symptom

was explosive, intractable, unproductive coughing, which was aggravated by excitement, deep breathing, or when lying on the back. The temperature often reached 38.4° C. (101° F.) but soon became normal when the child was put to bed. Whistling noises were heard in the lungs with loud bronchi at the bases. Roentgenograms showed only soft, patchy mottling with increased markings along the course of the bronchi. Treatment was symptomatic with sedatives and an expectorant cough mixture.

## COMPLICATIONS OF ASTHMA

Francis<sup>30</sup> stated that subcutaneous emphysema complicating asthma is not common; only nineteen cases have been previously recorded in the literature. To these the author added two cases of his own. One was a girl thirteen years of age who had had bronchial asthma since early childhood. The episode complicated an attack of asthma following an upper respiratory infection. She was dyspneic and cyanotic with moderate swelling at the base of the neck due to subcutaneous emphysema. This was confirmed by a roentgenogram. The emphysema disappeared after ten days. The mechanism seems to be as follows: during asthma the bronchus is plugged because of spasm, edema and mucus. This acts as a valvular mechanism allowing the air to enter the alveolus, but hinders its exit during expiration. The intra-alveolar pressure is thus increased with rupture during a violent coughing spell. The free air then follows the reflections of the pleura, pericardium or perivascular tissue, to the posterior mediastinum, et cetera.

A case of bilateral spontaneous pneumothorax in a sixteen-year-old girl was described by Davidson and Brock.<sup>15</sup> She had had asthma since the age of three years. A left-sided spontaneous pneumothorax occurred which subsided but recurred four months later followed by a collapse of the right lung. A month later the roentgenogram showed a bilateral pneumothorax. Silver nitrate was introduced into both pleural cavities to promote adhesions.

A detailed discussion of the mechanism whereby air is found in extra-pulmonary spaces as a complication of bronchial asthma is given by Derbes, Engelhardt and Sodeman.<sup>20</sup>

## TREATMENT OF ASTHMA

Holt<sup>41</sup> stated that the burning of asthma powders (stramonium leaves) occasionally produces satisfactory results. In asthmatic attacks in children which commonly follow upper respiratory infections the elimination of chronically infected pharyngeal tissue which cannot be treated surgically may be accomplished by radon. Where no such cause is evident and the respiratory infections are frequent and the asthmatic attacks severe, resort is sometimes had to the same treatment used for preventing recurrences of rheumatic fever; a small dose of sulfadiazene, 0.5 to 1.0 grams a day. That this procedure may be very useful is indicated by the report of Hodges<sup>40</sup> who used sulfadiazene as a prophylactic measure against respiratory disease in an army camp with very beneficial results. I have had a limited but highly favorable experience with this procedure in my own practice. Holt also states that Vitamin C may possibly be of some benefit in hay fever. My own experience cannot confirm this and recently published work rather definitely indicates that Vitamin C is of absolutely no value in pollinosis.<sup>36,31</sup>

The value of vaccine therapy in asthma is subject to perennial question. Stoesser<sup>67</sup> reported on a study of 214 children with allergic rhinitis or bronchial asthma or both which he followed for a period of two to four years. The children ranged in age up to sixteen years, although most were between six and ten years. In these patients the histories very clearly showed association of symptoms of acute respiratory infection with the allergic manifestations. Of the group there were fifty-nine who either did not respond to surgical procedures or who failed to give satisfactory reactions to the diagnostic allergenic extracts. In many of these chil-

dren, there was additional evidence in favor of infection as a primary cause of the attacks of allergic disease. There was no consistent response on testing with the bacterial allergens. Some patients with positive skin tests gave poor clinical results; some with negative tests gave good results. Eleven patients received autogenous vaccines with poor results. Stock vaccines were used in twenty-one cases with somewhat better results. The undenatured bacterial antigens of Krueger<sup>45</sup> were used in twenty-seven cases. Thirteen children showed remarkable improvement; nine gave a fairly satisfactory response and five were failures. Stoesser feels that the patients who improved could have had a specific response to this form of therapy; that autogenous vaccines may possibly have value if prepared from uncontaminated material secured through the bronchoscope as described by Crump<sup>14</sup> and that stock vaccines produce their results through nonspecific reactions.

Based on the theory that intrinsic allergy is of bacterial origin, Schonwald and Deppe<sup>63</sup> treated eighty-six cases of intrinsic bronchial asthma with a penicillin preparation. Forty-one patients were improved by this treatment. Eleven illustrative case histories were reported and these included three in children, five, seven and nine years of age respectively. The authors state that when their own preparation was used, subcutaneous treatments were given daily or every other day. Commercial penicillin was used in thirteen cases; 2500 units were given intramuscularly three times weekly. It is extremely difficult to understand how penicillin given in the doses mentioned by authors could have any beneficial effects, particularly in view of the rapid elimination of penicillin in the urine. Since their report, a paper reporting failure of penicillin in the treatment of intrinsic asthma has been recorded.<sup>35</sup>

Archibald<sup>1</sup> studied forty-five consecutive asthmatic children over periods ranging from six months to three years. The average age of the patient was eight years. Eighteen children received ethylene disulphonate alone; eighteen were given injections of distilled water alone and nine children received both. No children were treated who had responded well to the usual procedures. Benefit was obtained in a number of instances, both from the ethylene disulphonate and from the distilled water. The author concluded that the clinical effect of both was the same, being a form of physiological stimulation or nonspecific therapy.

Weiser<sup>75,76</sup> has reported on the treatment of bronchial asthma by means of breathing exercises. His series included twenty-nine children and twelve adults who suffered from bronchial asthma and in whom the usual methods of treatment such as specific and nonspecific desensitization had failed. The treatments discussed were intensive breathing exercises only. The aims were: to correct the physical deformities produced by the asthmatic attacks; to restore the elasticity of the thorax which is often fixed and distended in these cases; to develop and strengthen weak muscles, especially those respiratory muscles which were not already hypertrophied; and to prevent such secondary effects as chronic bronchitis, bronchiectasis, pulmonary fibrosis, cardiac hypertrophy and myocardial damage.

The author reports the details of the treatment which consists of massage and various forms of exercise. The progress of the patient is followed by frequent studies of vital capacity. The end results of treatment in general are very good. While the adults usually improve, they never attain the vital capacity of healthy people of corresponding age and physique. In the case of children this commonly occurs. The author states that the exercises which he describes are indicated in all cases of bronchial asthma showing a low vital capacity and cramped superficial breathing with poor chest expansion and little use of the diaphragm. They are contra-indicated in advanced bronchiectasis, severe emphysema, heart disease, pulmonary tuberculosis and febrile conditions. The method is usually unsuccessful if used for short periods only. The exercises should always be prescribed and supervised by a physician.

## PROGRESS IN ALLERGY

Pediatric allergists are familiar with the fact that children with respiratory allergies should not go about with bare heads and bare legs in cold weather. The question arose as to the effect which going about in this manner might have on normal children. This was answered in the *Journal of the American Medical Association*<sup>54</sup> as follows:

"Controlled experiments on this subject seem to be lacking. Some years ago it was stylish for children to be bare legged and hatless in cold weather under the theory that it would harden them against colds. The effects did not substantiate this idea, and certainly most pediatricians are agreed that young children at least should be properly protected against unnecessary exposure of legs or heads in cold weather. There is some reason to believe that chilling of certain portions of the skin may effect a decrease in resistance to infection, at least in some persons. The scientific evidence for the exact relationship between such chilling and susceptibility to colds, however, is tenuous. Insult to the human body by allowing a completely unnecessary chilling does not seem like a practice which thoughtful physicians can recommend, although the fact that enormous numbers of people do expose themselves freely to cold suggests that this is harmful only infrequently."

It is quite possible that these exceptions occur when the child is allergic, either clinically or subclinically.

### URTICARIA

Derbes and Engelhardt<sup>18</sup> referring to the work of Sulzberger and Vaughn<sup>70</sup>, who proved that inhalant substances may cause allergic dermatoses, reviewed the other literature on this subject and added two new cases of their own, one of whom was a boy eleven years of age who would develop asthma and urticaria when exposed to the fumes of fresh paint. It was particularly interesting that whereas the asthmatic attacks were over with in twenty-four hours, the urticaria persisted three or four days after the momentary stimulus.

### ALLERGY OF THE CENTRAL SYSTEM

Rowe<sup>58</sup> has briefly reviewed the literature on this subject. These conditions usually but not necessarily occur in patients with a history of urticaria and especially of cutaneous swellings, as far as children are concerned. The author mentions case reports previously published by him of a boy with Jacksonian attacks due to egg allergy, of a girl with attacks of dizziness, irritability, generalized twitching and unconsciousness relieved by elimination from the diet of wheat, milk, egg and pepper; a boy with convulsive seizures and bronchial asthma due to pollen; and petit mal in a girl associated with nasal allergy due to animal emanations.

Clarke<sup>12</sup> describes the case of a child twenty-three months of age who had had convulsions for two months occurring several times a day. The child reacted on cutaneous testing to a number of foods and environmental factors. Recovery was complete on the elimination of these factors. The author states that he has many times seen infantile convulsions of allergic origin. He also reports two cases in children which had been diagnosed as idiopathic epilepsy and which responded to allergic therapy. In both instances other allergies were present. One behavior problem in a boy thirteen years of age with pollinosis responded to the elimination of several reacting foods.

### HUMAN DANDER

The interesting work of Simon on the allergen in human dander has been previously reviewed.<sup>32</sup> Simon<sup>64</sup> states that the existence of allergic activity in the human dander may be regarded as having been established by previous investigators and confirmed by his present studies. Allergy to human dander is often associated with atopic dermatitis. Simon presents evidence that the allergen is not a constituent present in stratified squamous epidermis in general and that it does not have its



origin in accidental contamination of dander with suspended dust particles from the air. The fact that patients who are allergic to human dander give positive skin reactions also to the scales of seborrheic dermatitis, is in agreement with the clinical observations that this disease is often associated with excessive dander. The allergen may possibly occur in human dander as a result of some physiologic maturation process specific to the scalp epidermis or may have its origin in some micro-organism living, but not always pathogenic, on the scalp.

## DRUGS

In the previous review<sup>32</sup> demerol was discussed and it was stated that the properties of this new drug are such that it would doubtless have considerable value in asthma. It was further noted that no report of the dosage to be used in children had yet appeared in the American literature. Sprockhoff in Germany<sup>65</sup> recommends demerol in the croup of measles and diphtheria and pseudocroup. He believes that in some instances in these conditions by relaxing spasm tracheotomy may be avoided. While it is difficult to stop the cough in pertussis, its frequency and severity may be minimized. Demerol suppositories by night and demerol by mouth before meals will diminish the vomiting. He states that in general, vomiting is favorably influenced by demerol whether its origin is central or peripheral. The dosage advised by Sprockhoff is as follows: Infants, 2 to 4 gtts. by mouth, or a 25 mg. suppository or 0.10 to 0.20 c.c. subcutaneously; older children, 5 to 8 drops by mouth, or a 50 mg. suppository or 0.20 to 0.40 subcutaneously; larger children may receive 8 to 12 drops by mouth, or a 75 mg. suppository, or 0.50 c.c. to 0.80 c.c. subcutaneously. The solution of demerol used orally by Sprockhoff was a 5 per cent flavored aqueous solution not available in this country. Suppositories also are not available here.\* The preparation he used subcutaneously is the same as that used in this country. Sprockhoff has observed that the younger the child, the more is the sedative effect.

In my personal experience, I have found demerol in combination with epinephrine hydrochloride very effective in the treatment of asthma in infants and children; more so, in my opinion, than in adults. Demerol is supplied in 2 c.c. vials containing 100 mg. each. I use the demerol and epinephrine hydrochloride solutions mixed together in the same syringe, a procedure commonly employed by others. A conservative hypodermic dose of demerol is 1.5 mg. per kgm. (or 0.015 c.c. of the solution per pound). The tolerance of infants for demerol is doubtless quite high. This was illustrated by a child with meningitis complicating an inoperable meningomyelocoele. The child weighed 2280 gm. (5 pounds). For the relief of pain he was given 25 mg. of demerol (0.50 c.c.) by hypodermic without any apparent ill effects. This is a dosage somewhat in excess of 10 mg. per kgm. This was given without harm despite the fact that the intracranial pressure was increased, as evidenced by a bulging fontanelle, a condition in which demerol is said occasionally to produce very undesirable results.<sup>34</sup> Death occurred after the accidental administration of 220 mg. to a 6.5 kgm. (14 pounds) infant suffering from inoperable intestinal anomalies accompanied by obstruction, perforation and localized peritonitis. Within ten minutes after administration of the demerol, the child developed a patchy cyanosis and this was followed by what appeared to be respiratory arrest and death.

In infants weighing 3.6 kgm. (8 pounds) or more with severe colic not relieved by phenobarbital in the usual doses of 15, 30, or 45 mg. ( $\frac{1}{4}$ ,  $\frac{1}{2}$ , or  $\frac{3}{4}$  grains), I have frequently used one-half to three-quarters of a 50 mg. tablet orally with very good results and no undesirable side reactions. This is somewhat larger than the oral dosage recommended above by Sprockhoff.

\*Personal communication from the Winthrop Chemical Co., New York, N. Y.

## PROGRESS IN ALLERGY

In the previous review<sup>32</sup>, reference was made to the use of aminophyllin in suppositories as suggested by Dees<sup>17</sup> and it was suggested that if the patient is sensitive to chocolate (cocoa) it would be advisable to use some base besides cocoa butter for the suppositories. In response to inquiries as to what to use for a suppository base instead of cocoa butter, a suppository made of glycerinated gelatin (U.S.P.) may be used. In my own practice I have used as a suppository base propylene glycol monostearate,\* and have found this very satisfactory.

### PAREGORIC

Despite the fact that within recent years paregoric has been considered an unnecessarily complex mixture whose only virtue lies in the opium alkaloids which it contains, many pediatricians have continued to use paregoric for dry cough because of a feeling, based upon experience, that it is particularly useful in these conditions. An interesting study of the expectorant action of paregoric has been recorded by Boyd and MacLachlan.<sup>8</sup> They reviewed the history of paregoric and noted that Dr. Le Mort, a professor of chemistry at the University of Leyden from 1702 to 1718, is generally given credit for its origination. Under the name of "elixir asthmaticum" it became official in the London Pharmacopoeia of 1721. In the London Pharmacopoeia of 1746, the name was changed to "elixir paregoricum," a name which is still used as a synonym for paregoric. However, as a result of still further investigation into the history of the drug, the authors find it more logical to conclude that paregoric finally crystallized out of a welter of combinations of opium, dating back even to the Greeks, Romans, and Arabians, but especially to medical practice of the seventeenth to early nineteenth centuries.

By special methods of study, it was found that paregoric increased the output of respiratory tract fluid in various experimental animals and hence would probably have the same effect in man. What is most interesting is the fact that all the components of paregoric individually increase the output of respiratory tract fluid and when combined the ingredients have a more prolonged effect upon this output than that obtained by a summation of the individual ingredients. This was seen best in preparations of paregoric which had aged well over one year and which were of a dark brown color in contrast to the pale and light-brown color of nonaged preparations. Because of these experiments, the authors feel that they have provided laboratory evidence justifying the centuries-old use of paregoric in the treatment of dry, hacking coughs. Because of its marked expectorant action, paregoric is superior to morphine which probably has no expectorant action and to tincture of opium which has very little expectorant action.

### IDIOSYNCRASY

Meyer<sup>50</sup> reports the case of a boy seven years old with impetigo. Sulfathiazole ointment was used locally and sulfadiazine orally. After four and one-half grams had been given in one and one-half days, lesions which were probably petechiae appeared in the boy's skin. A day and a half later when a total of seven and one-half grams had been administered, the urine became bloody and after a total of nine grams in three days, hematuria became marked and the boy was hospitalized. The hemoglobin was reported as 23 per cent, red blood cells as 1.43, white blood cells as 23,850 with 86 per cent polymorphonuclear leukocytes, and the platelets were reported as 20,000. The boy was treated with repeated transfusions and discharged nineteen days after admission. The author briefly reviews two similar cases which terminated fatally, one a patient of seventy-nine years with pneumonia and another a patient of sixty with a postoperative infected hip.

Koteen<sup>44</sup> reported the case of a boy five and a half years old with tonsillitis who was started on sulfadiazine on the second day of illness. He received 0.75 gm.

\*Obtainable from the Goldschmidt Chemical Corp., 153 Waverly Place, N. Y.

every four hours for a total of nine grams, when the drug was discontinued because of absence of response. The next day the boy was hospitalized. On the third hospital day, the boy developed an acute morbilliform rash. He was treated with human convalescent scarlet fever serum without response. Penicillin therapy was then started. The throat symptoms and cervical lymphadenitis subsided but the boy's condition became critical. He was semi-conscious with a spiking fever and generalized edema. It seemed evident that the penicillin was not influencing the general course of the disease. On the eighth hospital day it was noted that the boy's blood did not clot in a test tube. At that time the prothrombin level was 54 per cent of normal and the platelet count 8,000. A diagnosis of sulfadiazine sensitivity with thrombocytopenia and severe toxic symptoms seemed justified. The sulfadiazine level was 2.3 mg. four days after the drug was discontinued. The boy improved on direct transfusion but on the eighteenth day developed granulocytopenia. He was given 2 c.c. of liver extract and 10 c.c. of pentnucleotide daily for eight days. Improvement was steady and he was discharged on the thirty-seventh hospital day, clinically well except for the persistence of hepatosplenomegaly. The history obtained after discharge indicated that on two previous occasions, the boy had had disagreeable reactions to sulfadiazine and sulfathiazole. This point would emphasize the importance of careful history taking in any child who is to receive sulfonamide therapy. The author emphasized also that hepatosplenomegaly rarely occurs after sulfonamide therapy. There is also mentioned the case of a boy five years of age who following sulfadiazine therapy developed a picture resembling the Waterhouse-Friedrichsen syndrome, with diffuse hemorrhage into the skin, shock and low platelet count. Necropsy showed massive hemorrhages into the adrenals.

A most unusual reaction to a single dose of 16 mg. ( $\frac{1}{4}$  gr.) of ephedrine sulphate in a boy 14 years of age is reported by Engelsher.<sup>24</sup> The history contained a note of extensive skin changes which appeared after one dose of ephedrine. For that reason epinephrine by hypo was used for relief. The statement in the first paragraph of the case report that the boy was receiving frequent injections of ephedrine is an error, as what was meant was epinephrine hydrochloride.\* Since the boy had received no ephedrine for several years, the mother suggested the possibility of the loss of ephedrine allergy, in which case its administration might reduce the necessity of so many injections of epinephrine hydrochloride. This seemed reasonable, so the mother was instructed to give the boy a 16 mg. dose of ephedrine sulphate. Eight hours afterward, red, edematous, itching areas developed in various parts of the body and eighteen hours afterward marked angioneurotic edema of the lips had developed. Any contact with the affected areas produced pain. A few days later, the corners of the mouth became fissured and the acute manifestations began to subside. However, for many weeks later, ridging of the finger nails persisted with desquamation of the affected skin areas. It required several months for the skin and finger nails to return to normal. It is very interesting that in this case, local cutaneous tests with ephedrine sulphate were negative. The author emphasizes the rarity of such reactions to ephedrine, especially the ridging of the nails. He also emphasizes the fact which so often requires emphasis, that before prescribing, an inquiry as to drug sensitivity should be made, particularly in allergic individuals.

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### Penicillin Urticaria

*(Continued from Page 361)*

In Table II are presented the skin responses which paralleled the clinical manifestations of urticaria. During the reactive phase, commercial penicillin sodium produced both urticaria and positive intradermal and positive passive transfer tests. After the reactive phase it had no effect. Attempts to obtain positive skin and ophthalmic tests and positive transfer with impurities of commercial penicillin sodium and crystalline penicillin sodium also failed after termination of the reactive phase. Penicillium extract injected intradermally caused no reaction in either the reactive or the non-reactive phase.

#### COMMENT

This case demonstrates that not only the penicillin urticaria but also the positive skin tests and positive passive transfer may be temporary. Whether or not the gradually diminished doses were responsible for the change or whether it occurred spontaneously cannot be stated. However, the results seem to warrant a trial of graduated doses of penicillin for desensitization in cases of severe penicillin urticaria.

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# \* In Memoriam \*

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## R. C. LOWDERMILK

1872—1945

With the passing of Dr. R. C. Lowdermilk of Galena, Kansas, the medical profession has lost one of the first physicians in America to treat pollen hay fever and asthma with graduated doses of pollen extract. His work coincided with that of Dr. Karl K. Koessler, but was antedated by the English observers Noonan and Freeman.

The many people who were attracted to Doctor Lowdermilk as a physician, teacher or as a philosopher, have lost a friend who will be difficult to replace.

Doctor Lowdermilk was born in Asheville, North Carolina, in 1872. He was educated in a normal training school in Kansas. Afterwards he taught in the public schools until he studied medicine at the University Medical College of Kansas City, Missouri, graduating in 1898. He practiced general medicine until 1913, after which time he specialized in the treatment of hay fever and asthma. Patients came to him from far and near.

When I met Doctor Lowdermilk in about 1913, he was well along with the study of pollen therapy for the treatment of hay fever and asthma. At about that time he gave up his practice in Galena for a few months to work on the subject in the laboratories of the University of Kansas in Rosedale, Kansas. He had been attracted to the work on "Protein Sensitization" of Dr. Victor Vaughan of Ann Arbor, and was trying to repeat some of Vaughan's experiments by splitting the proteins of pollen, hoping to make them less toxic to human beings.

He told me at that time that he had completely cured himself of ragweed hay fever, by the injection of a suspension of ragweed pollen, but that he had nearly killed himself in doing so. He said that he had relieved a number of patients by the same method of treatment, but that he was afraid he had shortened his own life trying to stop the reactions caused by the pollen extract. He said he was satisfied that pollen therapy offered a therapeutic method by which hay fever might be cured, but that a method must be found for reducing the severity of the reactions produced. He said he had relieved himself by pollen injections to such an extent that he could actually gather ragweed pollen without displaying symptoms of hay fever.

Doctor Lowdermilk's work with pollen started in the summer of 1911. He was author of one original paper, "Hay Fever," published in the *Journal of the A.M.A.* in July, 1914. This, unfortunately, was his only publication. However, he took an active part in the work of the state and county medical societies, reading many papers on the subject of pollen therapy. The doctor had a well-equipped laboratory, collected his own pollens and made his own extracts. He also had a method of testing which was all his own. He would employ a platinum hypodermic needle provided with a metal adapter, which he had made himself. He would sterilize the needle in a flame, dip it into the extract, and then scratch the patient's skin with it. At the end of the scratch, he would force the needle into the skin, thus making, at the same time, a scratch and an intracutaneous test. He said that by observing the two ends of the scratch he could gain information which he could use in deciding whether or not the patient was sensitive to the extract.

Doctor Lowdermilk gave me some of his extracts at a very early date and requested me to help him with this study. This and my personal liking for the doctor was responsible for my going into the study of allergy, to the extent that I did in the early days. Also, I think that I should have discontinued this work at an early pe-

riod had it not been for Doctor Lowdermilk's repeatedly saying: "Bill, this is the only method of treatment for the disease which we have."

Doctor Lowdermilk had a very interesting appearance and personality. He was a large, rather fleshy, man with long, wavy white hair and a large, round face. He had a very winning smile, which was always in evidence when he was with his friends. He gave the appearance of being a very happy man, fully content with his work and what he was accomplishing by it. He was an interesting reader, philosopher and conversationalist, and was well acquainted with the studies of Einstein. He loved to discuss Einstein's work and views. It seems to me unfortunate that a larger number of people could not have been acquainted with Doctor Lowdermilk and gain by his stimulating influence. He chose to do his work in a small town. He enjoyed the simple life in the country and could not be enticed from it, except for short periods of time. Many of us who knew him well will miss him deeply.

WILLIAM WADDELL DUKE, M.D.

### Asthmatic Attacks

(Continued from Page 365)

dioxide and oxygen pressure tank. The coughing up of these plugs of mucus relieves bronchial obstruction.

A small electric, mechanical aspirator can often be used after the above-mentioned procedure is employed. Long, tenacious plugs of mucus are often removed by the use of the mechanical aspirator.

#### SUMMARY

1. Suprarenalin hydrochloride, 1:100 glycerinized, plus 10 per cent carbon dioxide and 90 per cent oxygen used by means of the continuous inhalation method, will soon relieve severe attacks of asthma, increase the absorbing power of the bronchial mucosa, and help to liquefy sputum.

2. The carbon dioxide acts as an expectorant. This plus the bronchodilator action of the suprarenalin, and dryness preventive action of the glycerin in the solution helps the patient to cough up and expectorate mucus plugs.

60 N. West End Avenue

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# News Items

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Dr. G. Estrada de la Riva, Havana, Cuba, a member of the Editorial Staff of the ANNALS OF ALLERGY, registered for the Chicago instructional course.

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The second annual meeting of the American Academy of Allergy will be held in Chicago, Illinois, at the Palmer House, December 10 and 11, 1945. Detailed information may be obtained by writing the secretary, Dr. Karl D. Figley, 316 Michigan Street, Toledo 2, Ohio.

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There has been such a demand for bound volumes of the Progress in Allergy notes, which have appeared as comprehensive reviews of the literature on the various phases of allergy in the ANNALS, that the Editorial Board of the ANNALS is now having a limited number bound. Thus a very extensive bibliography and a brief review of the literature will be readily accessible to those interested in allergy as it applies to any particular specialty. An announcement will be made in the November-December issue concerning the price and when available.

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Inquiries are being received from many men interested or specializing in allergy, who are being discharged from active service, for information concerning likely locations for the practice of allergy. It would be appreciated if anyone knowing of a vacancy or a demand for an allergist in a clinic or elsewhere would please notify the Secretary of the American College of Allergists, 401 La Salle Medical Building, Minneapolis 2, Minnesota. The College is attempting to conduct a Bureau for the purpose of helping to re-locate its members or any other physicians interested in allergy.

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The editorial staff is establishing a new section in the ANNALS OF ALLERGY on Clinical Pathology. This will be under the direction of Dr. L. O. Dutton and will be limited to one or two pages. The discussions will be confined to well-recognized routine procedures, in an effort to stimulate more use of such in the study of the allergic individual. In the course of time the staff hopes to include a discussion of the theory and application of the more complicated tests. From time to time simple diagnostic procedures, as well as accepted therapeutic procedures which may have been overlooked, will be published.

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## Membership

Membership in the College so far is: Active Fellows 400; Associate fellows 67; Honorary Fellows 15; Corresponding Fellows 2. Another group will be considered for membership at the meeting of the Board of Regents to be held in Chicago, Illinois, Sunday, November 4, 2:30 p.m., at the Knickerbocker Hotel.

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## Additional Funds for Research in Allergy

Luzier's, Inc., Kansas City, Missouri, has made a grant of \$1,500 to the College to be used for a research fellowship for one year. This will be known as the Luzier Grant for Fundamental Investigations in the Field of Dermatologic Allergy. The fellowship will be under the direction of Dr. Rudolf Baer, New York City, and Dr. Stephan Epstein, Marshfield, Wisconsin. The College is deeply grateful for the establishment of this Fellowship by Luzier's, Inc., in accepting such a worthy gift.



## INTERNATIONAL ASSOCIATION OF ALLERGISTS

The International Association of Allergists, whose aims and purposes and plans were briefly announced in the July-August issue of the *ANNALS* has now been incorporated, without profit, and the Constitution and By-Laws adopted by the officers until the first meeting of the Association.

The general purposes of this Association are educational, scientific, and medical, and in particular for the advancement of the study, research, and clinical knowledge of allergy as it applies to the various specialties of medicine.

The active membership shall be open to physicians of good standing in the medical profession who are engaged as practitioners in the field of allergy. Membership in, or possession of the qualifications necessary for admission to, any organized allergy group which is a member of, or is affiliated with, or is accredited by, this Association, shall be taken, in the discretion of the Board of Regents, as sufficient proof of qualification as an allergist. Associate membership shall be open to physicians of good standing in the medical profession who apply allergy in their practice, and to any scientific student of the subject of allergy, and to any person engaged as a scientist or student of allied subjects. Honorary membership shall be limited to those persons having the qualifications of active or associate members and who shall be specially selected by the Board of Regents for outstanding and meritorious contributions in allergy and for eminence in their respective professions.

The general management of the affairs of this Association shall be vested in an Executive Committee composed of not less than three nor more than nine members, who, except the first Committee, shall be elected from and by the Board of Regents for a term of two years. The Executive Committee shall have the power to make and amend By-Laws for the government of this Association, subject to the approval of the Board of Regents.

The membership of this Association is divided into three classes: Active, Associate, and Honorary. The Board will provide appropriate certificates of membership and prescribe rules for their issuance. Candidates for Active membership shall be graduates of accredited medical schools and shall have done at least five years active practice in allergy and shall be not less than twenty-nine years of age at the time of application or nomination for membership. A written application form prescribed by the Board of Regents will be furnished candidates upon request. Supplemental information and evidence will be required as to the candidate's moral character and other qualifications, and he shall satisfy all other requirements imposed by the Articles and By-Laws of the Association. The Regents may require candidates to furnish and may consider among other things: hospital and academic appointments, personal acceptability to members in his territory, character, ethical standing, membership in medical societies, attendance at meetings of allergy groups, and membership in any such groups or other professional groups, and research or writings upon the subject of allergies and original investigations therein, and the quality and quantity of clinical reports with particular reference to the diagnostic and therapeutic summary in such matters.

Each nation and each of the self-governing dominions of the British commonwealth of which one or more of its nationals shall be active members of the Association, shall be entitled to one Regent and additional Regents, not exceeding a total of three Regents for any one nation or any of such dominions, to be selected or otherwise designated as follows: in any nation where there is no organized group of allergists which is a member of, or is affiliated with, or is accredited by, this Association, if there be only one active member of this Association, he shall, ipso facto, be the Regent for such nations, or if there be two or more such active members, they, or a majority of them, shall select the Regent; in nations where there is such a group of allergists, the Regent shall be selected by such a group; in nations where there are two or three of such groups, each group shall select a regent; and in nations where there are four or more such groups, the maximum number of three Regents shall be selected by the combined action of all such groups.

The Board of Regents shall have the power to appoint from among its own number an Executive Committee composed of not less than three nor more than nine members, which number shall include the officers of this Association, who ex officio shall be members of the Executive Committee. Between meetings of the Board of Regents, the Executive Committee may exercise all the powers of the Board, as permitted by law and in accordance with the policy of this Association and under the direction of the Board of Regents. The Board shall have the power to create

any additional committees and to prescribe their functions and duties, within the limitations of the Certificate of Incorporation and the By-Laws.

Regional or sectional meetings such as Pan-American and Pan-European Congresses or any other special meetings of the Association may be held at such times and places and under such conditions as the Board of Regents shall determine, either upon their own motion or upon the request of any twenty-five members; and all such meetings shall be open to all members. The officers shall consist of a president, vice president, secretary and treasurer and shall be elected from and by the Board of Regents for a two-year term and shall hold office until their successors have been elected and qualified. The officers shall, ipso facto, be members of the Executive Committee of this Association.

So far the Association has members from Argentina, Brazil, Uruguay, Chile, Guatemala, Mexico, Cuba, Australia, Canada, Great Britain, France, Switzerland, Russia, and the United States.

## INSTRUCTIONAL COURSES AVAILABLE

Printed sets of the comprehensive outlines of lectures, including references, of the Fall graduate instructional courses presented by the College at Northwestern University, Chicago, Illinois, November 5th to 10th inclusive, are available for \$6.00 a set. These are perforated to fit a standard ring book as formerly. Please mail orders to American College of Allergists, 401 LaSalle Medical Building, Minneapolis 2, Minnesota. Several lectures were stenotyped and copies of these will be included with the printed set.

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 J. WARRICK THOMAS, M.D., Vaughan Memorial Clinic, Richmond, Virginia

### The Conjunctival Test

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### The Future of American Medicine

(Continued from Page 372)

burdened with war responsibilities to give adequate consideration to basic problems, has contented itself with the sophistry "It can't happen here."

"It is happening—now. Wartime fervor and preoccupation and wartime confusion are being used to obscure the true meaning of the moves. The issue is being forced. The settlement will be final. Doctors—informed—understanding—unified—can be the deciding factor in this final determination."

This issue must be decided by the voter of the United States. Please take time out to talk or write to your senator and congressman and indicate that political domination of medical progress will precipitate a medical revolution.

F. W. W.

# ANNALS of ALLERGY

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## THE EXTRACTION OF NITROGENOUS MATTER FROM POLLENS

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THE whole problem of standardization has been discussed from many angles; and of all the types of standardization so far published, that of molar standardization which has been advocated by Rockwell<sup>18,19,20</sup> and others seems to be the most promising from a purely chemical standpoint. However, in order to apply this method, it is imperative that pure chemicals be used or at least mixtures whose compositions are accurately known. For molar solutions presuppose that a definite molar fraction of a pure homogeneous substance be dissolved in a known amount of solution. The whole problem of chemical standardization has been oversimplified. On the contrary, the problem is very complicated and one which will not be solved in a short time. The work that has been done by Abramson, Moore and Gettner<sup>1</sup>, Newell<sup>15</sup>, and Spies, Bernton and Stevens<sup>22</sup>, to mention but a few, has shown that extracts are exceedingly complicated mixtures which have to be painstakingly separated, the chemicals which cause the allergy identified, and finally a method must be evolved for estimating this substance or substances in the mixture. Many basic facts must be discovered before this system can be applied. Either methods must be found for isolating these chemical substances or, if this is impossible, then the mixtures must be capable of being analyzed for their antigens before the method can be used. Once these problems are solved, this chemical method will be much more satisfactory than a biological standardization.

Another reason for stressing the importance of pure homogeneous substances is that antigenic properties seem to be associated with specific chemicals. This fact has been strikingly illustrated in an article by Chow<sup>7</sup> wherein the author shows that the pituitary extract does not contain a single substance but is really composed of five different proteins each of which has a very definite physiological reaction.

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While it is true that an individual may react to many of the nitrogenous substances in a specific pollen, it does not follow that if an individual is sensitive to one of these compounds, he is therefore sensitive to all the nitrogenous compounds which are found in the substance and therefore the potency of the extract cannot be judged by its nitrogen or protein nitrogen content. In fact the opposite is generally the case, as has been proven by Bernton, Jones and Csonka<sup>2</sup>, Stull, et al.<sup>24</sup>, and Spies, Bernton and Stevens<sup>23</sup>, to mention but a few. Consequently the use of the protein nitrogen unit or the total nitrogen unit are unsatisfactory from a purely chemical standpoint. It is freely admitted, however, that they are a measure of protein or proteinoid content, but they do not give an accurate picture of the potency of that extract. Many of the apparent discrepancies which are found in the literature could be easily explained on this basis. For while one investigator, in making his extracts, may use one procedure, another may use a different extracting and purifying technique and therefore may obtain different clinical results. It would therefore seem necessary to do some basic research in this field of extraction so that these results may be explained on the basis of more complete knowledge. In this article some of these problems have been investigated.

In this investigation the following line of reasoning was used: if the nitrogenous organic compounds are responsible for sensitization, and it seems reasonable to agree with this conclusion in view of the experimental evidence, then these compounds can roughly be separated into groups on the basis of their solubility. This having been done and the extracts tested clinically then further fractionation can be made. Thus by repeatedly extracting with sodium chloride solution, all the nitrogenous compounds soluble in this medium could be extracted from pollen.\* These extracts would contain the following nitrogenous compounds: albumins, globulins, proteoses, peptones, polypeptides and amino acids. In this process repeated extraction would assure the investigator that subsequent extracts would not be contaminated with the above-mentioned compounds. Such an assurance could be obtained when the nitrogen content of the extracts dropped to a minimum. Once this condition has been obtained, then the pollen would be repeatedly extracted with 70 per cent ethyl alcohol, thus removing the prolamins. Again the extracts would be tested for their nitrogen content until it dropped to an insignificant figure. Finally this would be followed by repeated extraction with dilute alkaline, which would remove the glutelins. All these solutions would be tested clinically, and the extracts containing the antigens located.

If, as would be expected, the sodium chloride extracts contained most of the antigen or antigens, then a further fractionation of the compounds occurring in this portion of the extracts could be undertaken. In this fractionation procedure, care must be exercised not to change the chemical

\*The pollens were not defatted because (1) the defatting removes antigen<sup>12</sup>; (2) the authors wished to get the same type of extraction as is had in the body.

composition of the compounds. The separation of the globulins from the water-soluble compounds could conceivably be affected by dialysis, but, because of the diversity of results in the literature<sup>12,13,14,15</sup> and because of the difficulties experienced in preliminary experiments of this investigation, this method was rejected. Instead, the following method was adopted: fresh pollen was repeatedly extracted with water and after the nitrogen content of the extracts had dropped to a minimum, then sodium chloride solution was used to extract those compounds soluble in this medium. In this way it was possible to separate the globulins from the water-soluble compounds, and these in turn could be tested clinically. It might be well to note in passing that whenever the terms albumins, globulins, proteoses, peptones and polypeptides are employed, they are used in the sense laid down by the American Society of Biochemists.<sup>11</sup> These definitions may be summarized as follows<sup>12,21</sup>:

Albumins are those proteins which are soluble in water and dilute salts, coagulable by heat, and are usually deficient in glycine.

Globulins are insoluble in water, soluble in strong acids and alkalies, in neutral salts, and usually contain glycine.

Prolamines are soluble in 70-80% ethyl alcohol, yield a large amount of proline and amide nitrogen and are deficient in lysine.

Glutelins are heterogeneous mixtures of cell proteins obtained by alkali extracts of the residue after removal of the albumins, globulins and prolamines.

Proteoses are the hydrolytic decomposition products of the proteins. They are soluble in water, not coagulable by heat, and precipitated by saturation of their solutions with ammonium sulfate.

Proto-proteoses are precipitated by half saturation with ammonium sulfate.

Deutero-proteoses are precipitated by the full saturation of their solutions with ammonium sulfate.

Peptones are also hydrolytic decomposition products of the proteins. They are soluble in water, not coagulable by heat, not precipitated by saturation with ammonium sulfate, are generally diffusible and give the biuret reaction. They are precipitated by tannic acid.

Peptides are polymers of the amino acids. They are not heat coagulable.

#### POLLEN ANALYSIS

Three pollens were chosen for study, short ragweed, timothy, and Russian thistle. The first two were chosen so that a comparison could be made between the results obtained in this investigation and previous investigations. The latter was added because it was the cause of much hay fever in the Pacific Northwest and previously had not been investigated.

*Moisture Content*—All three pollens were dried to a constant weight so that the nitrogen determinations could be calculated on the dry basis. To accomplish this, the pollens were dried over concentrated sulfuric acid, at 70° C. and a pressure of about 20 mm. The pollens were weighed periodically as indicated in Table I and the heating was continued as long as there was any appreciable change in the weight of the pollens. The

TABLE I. PER CENT OF WEIGHT LOST AS MOISTURE

	TIMOTHY	RUSSIAN THISTLE	RAGWEED
After heating 3 hours	4.43%	5.37%	5.61%
After heating 24 hours	5.44%	5.64%	5.88%
After heating 48 hours	5.54%	5.65%	5.92%
After heating 72 hours	5.56%	5.68%	5.98%
After heating 96 hours	5.57%	5.68%	5.99%

pollens could be dried to a constant weight in about four or five days using this technique, as compared with months when the pollen was treated at ordinary temperatures and pressures. The apparatus used was a modified form of the Abderhalden apparatus, which has been described by Clark.<sup>5</sup> It is remarkable that all these pollens had moisture contents which were so nearly equal.

*Nitrogen Determination*—In order to determine the effectiveness of the various extracting media in removing the nitrogen, the dried pollens were analyzed for their nitrogen content. Thus the percentage of nitrogen removed in each of several successive extractions could be calculated. The semi-micro Kjeldahl method was used for these determinations. The procedure, as outlined by Clark<sup>6</sup>, was followed except that 40 mg. of pollen were used instead of the 10 mg. recommended. The catalyst was also modified. Instead of using mercuric oxide, a mixture of selenium, mercuric oxide, and copper sulfate was employed. This particular combination of catalysts was investigated and advocated by Poe and Nalder.<sup>17</sup> The semi-micro method is of advantage when the material to be analyzed is expensive. The time of digestion is cut down in this method. The three pollens analyzed had the following nitrogen content: timothy, 3.57 per cent, Russian thistle, 3.88 per cent and ragweed 3.66 per cent.

#### EXTRACTION

Ten grams of pollen were mixed with 90 ml. of extracting fluid, and the mixture was shaken mechanically in a closed container for twenty-four hours. The temperature was held at 32° C.  $\pm 1^\circ$ . This temperature was chosen because it has been known for some time that an extracting medium is much more effective if it is slightly warm. Osbourne<sup>16</sup> states that the degree of extracting noticeably increases around 30° C. Higher temperatures were avoided because of the danger of denaturation of the proteins. At the end of 24 hours the pollen was filtered with suction through a sintered glass filter of fine porosity. This type of filter gives a clear filtrate except in the case of ragweed, which extract, after removing the main bulk of the pollen on a glass filter, was refiltered through a Seitz pressure filter. The pollen was then suspended in 90

ml. more of extracting medium and the process, as described above, was repeated.

Altogether five 10 per cent sodium chloride extracts were made; this was followed by three extractions using 70 per cent ethyl alcohol and finally five extracts were made with a 0.2 per cent sodium hydroxide solution. A total of thirteen successive extractions were made on each pollen. In extracting with sodium hydroxide it was frequently necessary to refilter through a Seitz filter in order to clear the filtrates. Five extractions with 90 ml. of 10 per cent sodium chloride were sufficient to reduce the amount of nitrogen present to a minimum; the same was true with three ethyl alcohol extractions. With sodium hydroxide, however, five extractions were used but the nitrogen content of the extracts was still fairly high. But as no extractions were to follow these extractions, no erroneous results could follow due to incomplete removal of interfering antigens.

Finally, new samples of pollen were extracted with distilled water in the same proportions as described above. The same method as outlined above was also followed. Five such water extracts were made; at this point the nitrogen content of the extracts fell to a minimum. One further extract was made from the water-extracted pollen with a 10 per cent solution of sodium chloride. Chemicals of reagent grade were used throughout these experiments.

*Analysis of the Extracts*—All extracts were tested for their total nitrogen and protein nitrogen content. Semimicro procedures were used throughout. For the determination of total nitrogen, a 1 ml. sample was digested with 40 mg. of mercuric oxide, 10 mg. of copper sulfate, a small Hengar crystal, 0.5 gm. of potassium sulfate and 1.5 ml. of concentrated sulfuric acid. The digestion was allowed to proceed for approximately an hour and a half; the sample was then removed from the digester, cooled and 8 ml. of distilled water was added. This mixture was then quantitatively transferred to the steam distillation apparatus. Seven ml. of 40 per cent sodium hydroxide containing 5 per cent sodium thiosulfate were added and steam was passed through the apparatus. The condensate was collected in a 25 ml. Erlenmeyer flask containing 2 ml. of 4 per cent boric acid and one drop of methyl red, the latter being used as an indicator. After approximately 8 ml. had distilled over, this mixture was titrated with .01 N. hydrochloric acid. A definite pink color was taken as the end point in the titration. Semimicro burettes reading to 1/100 ml. were used. The use of boric acid as an absorbent for ammonia proved very satisfactory as the boric acid retained the ammonia without interfering with the acid titration. Its use has been extensively investigated and has been found entirely satisfactory.<sup>31</sup>

In order to determine the protein nitrogen, the protein was precip-



TABLE II. TIMOTHY

Extract No.	10% NaCl Extraction				
	Total N <sub>2</sub> mg. per ml.	Total N <sub>2</sub> in 90 ml.	%Total N <sub>2</sub> extracted	Protein N <sub>2</sub> mg. per ml.	Total Protein N <sub>2</sub> in 90 ml.
1	1.742	156.9 mg.	46.50 %	.7780 mg.	70.00 mg.
2	.120	10.8 mg.	3.21 %	.0892 mg.	8.02 mg.
3	.079	7.1 mg.	2.11 %	.0344 mg.	3.09 mg.
4	.042	3.8 mg.	1.13 %	.0204 mg.	1.83 mg.
5	.033	2.9 mg.	.86 %	.0204 mg.	1.83 mg.
Total		181.5 mg.	53.81 %		84.77 mg.
	70% Ethyl Alcohol Extraction				
	Total N <sub>2</sub> mg. per ml.	Total N <sub>2</sub> in 90 ml.	%Total N <sub>2</sub> extracted	Protein N <sub>2</sub> mg. per ml.	Total Protein N <sub>2</sub> in 90 ml.
1	.033	2.9 mg.	.86 %	.0255 mg.	2.29 mg.
2	.015	1.4 mg.	.42 %	.0000 mg.	.00 mg.
3	.013	1.2 mg.	.33 %	.0000 mg.	.00 mg.
Total		5.4 mg.	1.61 %		2.30 mg.
	.2% NaOH Extraction				
	Total N <sub>2</sub> mg. per ml.	Total N <sub>2</sub> in 90 ml.	%Total N <sub>2</sub> extracted	Protein N <sub>2</sub> mg. per ml.	Total Protein N <sub>2</sub> in 90 ml.
1	.555	50.0 mg.	14.83 %	.548 mg.	49.30 mg.
2	.343	30.9 mg.	9.17 %	.324 mg.	29.15 mg.
3	.345	31.0 mg.	9.18 %	.172 mg.	15.49 mg.
4	.158	14.2 mg.	4.21 %	.124 mg.	11.16 mg.
5	.129	11.6 mg.	3.44 %	.105 mg.	9.45 mg.
		137.7 mg.	40.83 %		124.60 mg.
Grand Total		324.6 mg.	96.25 %		211.67 mg.

itated with phosphotungstic acid in the presence of hydrochloric acid. A 2 ml. sample was treated with a 10 per cent solution of phosphotungstic acid in 10 per cent hydrochloric acid and concentrated hydrochloric acid; the solution was permitted to stand for two hours, was centrifuged and the supernatant fluid tested for complete precipitation. This step is important as the usual quantities of reagents called for by many standard procedures were found to be insufficient for complete precipitation. Thus Vaughan, in his book, *The Practice of Allergy*<sup>31</sup>, calls for a ratio of 0.1 ml. of 10 per cent phosphotungstic acid to each ml. of extract. It was found in this investigation that a ratio of 1 ml. to 1 ml. was needed for complete precipitation of the more concentrated extracts. After complete precipitation, the mixture was centrifuged and the supernatant liquid discarded. The precipitate was washed three times with phosphotungstic-hydrochloric acid wash solution, centrifuged and the washing discarded. The precipitate was then dissolved in a small amount of 5 N. sodium hydroxide and quantitative transferred to a digestion flask. The solution was digested as in the total nitrogen determination, the resulting solution made alkaline and distilled as described above. Blanks were run on all determinations to check the purity of the chemicals used.

## EXTRACTION OF NITROGENOUS MATTER—STIER, ET AL

TABLE III. RUSSIAN THISTLE

Extract No.	10% NaCl Extraction				
	Total N <sub>2</sub> mg. per ml.	Total N <sub>2</sub> in 90 ml.	%Total N <sub>2</sub> extracted	Protein N <sub>2</sub> mg. per ml.	Total Protein N <sub>2</sub> in 90 ml.
1	1.655	149.0 mg.	43.2%	.993	89.3 mg.
2	.271	24.4 mg.	7.1%	.085	7.7 mg.
3	.103	9.3 mg.	2.7%	.037	3.3 mg.
4	.050	4.5 mg.	1.3%	.020	1.8 mg.
5	.018	1.6 mg.	.5%	.009	.8 mg.
Total		188.8 mg.	55.0%		102.9 mg.
	70% Ethyl Alcohol Extraction				
	Total N <sub>2</sub> mg. per ml.	Total N <sub>2</sub> in 90 ml.	%Total N <sub>2</sub> extracted	Protein N <sub>2</sub> mg. per ml.	Total Protein N <sub>2</sub> in 90 ml.
1	.027	2.4 mg.	.7%	.024	2.2 mg.
2	.014	1.3 mg.	.4%	.013	1.2 mg.
3	.009	.8 mg.	.2%	.011	1.0 mg.
Total		4.5 mg.	1.3%		4.4 mg.
	.2% NaOH Extraction				
	Total N <sub>2</sub> mg. per ml.	Total N <sub>2</sub> in 90 ml.	%Total N <sub>2</sub> extracted	Protein N <sub>2</sub> mg. per ml.	Total Protein N <sub>2</sub> in 90 ml.
1	.538	48.4 mg.	14.0%	.493	44.3 mg.
2	.167	15.0 mg.	4.3%	.144	12.9 mg.
3	.112	10.1 mg.	2.9%	.065	5.8 mg.
4	.092	8.3 mg.	2.4%	.070	6.3 mg.
5	.116	10.4 mg.	3.0%	.099	8.1 mg.
Total		92.2 mg.	26.6%		77.4 mg.
Grand Total		285.5 mg.	82.90%		184.7 mg.

## DISCUSSION OF ANALYTICAL RESULTS

The analytical results of these experiments are given in Tables II, III, IV, and V. The first column of these tables lists the number of the extract and the second the total nitrogen content of the extract expressed in mg. per ml. The third column shows the amount of total nitrogen extracted in 90 ml. of extract. The fourth column indicates the percentage of nitrogen, originally present in the pollen, which was extracted by each solution. The fifth column gives the protein nitrogen content of the extract in mg. per ml., and finally the sixth column the total amount of protein nitrogen which was extracted in 90 ml. of extracts. Table VI gives a summary of the results outlined in Tables II, III, IV and V.

It is interesting to note that although the percentage of nitrogen (originally present in the pollen) which was extracted, varies considerably, i.e., 96.25 per cent for timothy, 82.90 per cent for Russian thistle, and 64.70 per cent for ragweed, yet in the total amount of nitrogen which was extracted, the percentage of protein nitrogen is quite constant, amounting to 65.2 per cent for timothy, 64.6 per cent for Russian thistle and 66.2 per cent for ragweed. It might be mentioned in passing that this result is at variance with that obtained by Moore and Moore<sup>14</sup> who state that most of the nitrogen in the pollen is in the form of nonprotein nitrogen. The

## EXTRACTION OF NITROGENOUS MATTER—STIER, ET AL

TABLE IV. SHORT RAGWEED

Extract No.	10% NaCl Extraction				
	Total N <sub>2</sub> mg. per ml.	Total N <sub>2</sub> in 90 ml.	% Total N <sub>2</sub> extracted	Protein N <sub>2</sub> mg. per ml.	Total Protein N <sub>2</sub> in 90 ml.
1	1.349 mg.	121.3 mg.	33.4%	.675 mg.	60.7 mg.
2	.285 mg.	25.6 mg.	7.0%	.324 mg.	29.1 mg.
3	.089 mg.	8.0 mg.	2.2%	.044 mg.	4.0 mg.
4	.039 mg.	3.5 mg.	1.0%	.006 mg.	.5 mg.
5	.024 mg.	2.2 mg.	.6%	.000 mg.	.0 mg.
Total		160.6 mg.	44.2%		94.3 mg.
	70% Ethyl Alcohol Extraction				
	Total N <sub>2</sub> mg. per ml.	Total N <sub>2</sub> in 90 ml.	% Total N <sub>2</sub> extracted	Protein N <sub>2</sub> mg. per ml.	Total Protein N <sub>2</sub> in 90 ml.
1	.124 mg.	11.2 mg.	3.1%	.101 mg.	9.1 mg.
2	.048 mg.	4.3 mg.	1.2%	.024 mg.	2.2 mg.
3	.031 mg.	2.8 mg.	.8%	.005 mg.	.5 mg.
Total		18.1 mg.	5.1%		11.8 mg.
	.2% NaOH Extraction				
	Total N <sub>2</sub> mg. per ml.	Total N <sub>2</sub> in 90 ml.	% Total N <sub>2</sub> extracted	Protein N <sub>2</sub> mg. per ml.	Total Protein N <sub>2</sub> in 90 ml.
1	.158 mg.	14.2 mg.	3.9%	.189 mg.	17.0 mg.
2	.120 mg.	10.8 mg.	3.0%	.084 mg.	7.6 mg.
3	.117 mg.	10.5 mg.	2.9%	.092 mg.	8.2 mg.
4	.115 mg.	10.3 mg.	2.8%	.092 mg.	8.2 mg.
5	.113 mg.	10.2 mg.	2.8%	.090 mg.	8.1 mg.
Total		56.0 mg.	15.4%		49.1 mg.
Grand Total		234.7 mg.	64.70%		155.2 mg.

results here listed show that approximately two-thirds of the nitrogen present in the pollen is in the form of protein nitrogen.

Another interesting feature, which seems to have been overlooked in the work which has been done so far, is the fact that water is a more efficient extracting medium for total nitrogen than sodium chloride. Even in the case of protein nitrogen, more of this material is removed by the water than is removed by the sodium chloride, at least in the case of timothy and ragweed. This is unexpected as the opposite would be predicted on purely theoretical grounds, as the sodium chloride solution should remove all the organic nitrogenous compounds extracted by water plus the globulins, which are soluble in sodium chloride solution but not in water. But the opposite is the case. The cause for this discrepancy is not clear.

It would be interesting to see the quantitative clinical data on the relative potency of water extracts and sodium chloride extracts because if such data were at hand it might completely settle the question of the absolute value of the total-nitrogen unit and the protein-nitrogen unit as norms in standardization. If the water extract, say that of timothy, was more antigenic than the saline extract then it would confirm the use of the protein-nitrogen unit and the total-nitrogen unit because the water extract contains more of these two substances than the saline extract.

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TABLE V

Extract	Total N <sub>2</sub> mg. per ml.	Total N <sub>2</sub> in 90 ml.	% Total N <sub>2</sub> extracted	Protein N <sub>2</sub> mg. per ml.	Total Protein N <sub>2</sub> in 90 ml.
Water Extraction TIMOTHY					
1	1.823 mg.	164.1 mg.	48.7%	1.487 mg.	133.9 mg.
2	.504 mg.	45.3 mg.	15.0%	.161 mg.	14.5 mg.
3	.239 mg.	21.5 mg.	6.4%	.064 mg.	5.6 mg.
4	.139 mg.	12.5 mg.	3.7%	.034 mg.	3.1 mg.
5	.074 mg.	6.7 mg.	2.0%	.029 mg.	2.6 mg.
Total		250.1 mg.	75.8%		159.7 mg.
Salt Extraction	.120 mg.		3.2%	.067 mg.	6.0 mg.
Water RUSSIAN THISTLE					
1	1.722 mg.	155.0 mg.	44.9%	.541 mg.	48.7 mg.
2	.341 mg.	30.7 mg.	8.9%	.057 mg.	5.1 mg.
3	.316 mg.	28.5 mg.	8.3%	.044 mg.	4.0 mg.
4	.131 mg.	11.8 mg.	3.4%	.022 mg.	2.0 mg.
5	.094 mg.	8.5 mg.	2.5%	.000 mg.	.0 mg.
Total		234.5 mg.	68.0%		59.8 mg.
Salt 1	.143 mg.	12.8 mg.	3.7%	.038 mg.	3.4 mg.
Water RAGWEED					
1	1.683 mg.	151.5 mg.	41.7%	1.298 mg.	116.7 mg.
2	.366 mg.	33.0 mg.	9.1%	.128 mg.	11.6 mg.
3	.113 mg.	10.3 mg.	2.8%	.061 mg.	5.5 mg.
4	.081 mg.	7.3 mg.	2.0%	.038 mg.	3.4 mg.
5	.070 mg.	6.3 mg.	1.7%	.006 mg.	.5 mg.
Total		208.4 mg.	57.3%		137.7 mg.
Salt 1	.127 mg.	11.4 mg.	3.1%	.071 mg.	6.4 mg.

TABLE VI. SUMMARY

	TIMOTHY	RUSSIAN THISTLE	RAGWEED
Mg. of nitrogen present in 10 gm. of pollen	337.0 mg.	344.5 mg.	363.2 mg.
Mg. of nitrogen extracted in 13 extractions	324.6 mg.	285.5 mg.	234.7 mg.
Per cent of the nitrogen extracted	96.25%	82.90%	64.70%
Mg. of protein nitrogen extracted in 13 extractions	211.7 mg.	184.7 mg.	155.2 mg.
Per cent of protein nitrogen in the nitrogen extracted	$\frac{211.7}{324.6} = 65.2\%$	$\frac{184.7}{285.5} = 64.6\%$	$\frac{155.2}{234.7} = 66.2\%$
Per cent of non-protein nitrogen	100-65.2= 34.8%	100-64.6= 35.4%	100-66.2= 33.8%

But if the saline extract was clinically stronger (this seems to be the case as will be brought out in the discussion of clinical results), then it would show that the protein-nitrogen unit and the total-nitrogen unit antigenically do not give a true picture of the strength of an extract, because both the total nitrogen and the protein nitrogen are higher in the case of the water extract.

#### CLINICAL EXPERIMENTS

All extracts were tested clinically in order to find if these various fractions were capable of giving skin reactions, i.e., wheals. The scratch method of testing was used exclusively and no quantitative results are claimed. The authors were interested in the separation of the various chemicals by solubility and these solutions were tested to find where the skin-exciting chemicals were located. *The tests were made on the patient's back in order to obtain a region of even and high sensitivity. This location also afforded an area sufficient for the large number of tests which had to be carried out on each individual.*

Since from previous investigations in this field, it was suspected that most of the antigen would be concentrated in the 10 per cent sodium chloride extracts these five successive extracts were all tested. The first of the alcohol extracts and the first of the sodium hydroxide extracts were likewise tested at the same time. Together with these solutions, a control glycerosaline extract was used. This latter type of solution is used in the routine testing of patients. Thus a qualitative check could be made on the sensitivity of the patients tested. If an individual reacted positively, say to the first, second, and third of the sodium chloride extracts and was negative to the fourth and fifth extracts, then it could be assumed that the following extracts would not have sufficient of the skin-exciting chemical which was extracted by the sodium chloride to give a subsequent reaction. If a wheal did develop with the other extracts, then it would be due to a new substance being extracted by the new extracting medium.

Because of the large class of chemical substances which could be extracted with 10 per cent sodium chloride, a separation within this group was attempted. As stated previously, a fresh sample of pollen was extracted with 5 successive portions of water in the manner outlined above. Then this water-extracted pollen was treated with a 10 per cent solution of sodium chloride. Thus the water extract would remove all the albumins, proteoses, peptones, polypeptides and amino acids (also much of the nonprotein nitrogen) and the subsequent sodium chloride treatment would extract the globulins and some of the remaining nonprotein nitrogen. The globulins would be contained in this fraction because from their very definition they are proteins which are insoluble in water but soluble in sodium chloride.

The first, the third, and the fifth water extract were tested clinically and also the first of the sodium chloride extracts. The tests were per-

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TABLE VII. TIMOTHY

Patient	Date	Control	1st NaCl	2nd NaCl	3rd NaCl	4th NaCl	5th NaCl	1st Alcohol	1st NaOH
1	2/20	+	+	+	+	0	0	0	0
2	2/20	++++	++++	++++	0	0	0	0	++
3	2/21	+	+	+	0	0	0	0	0
4	2/25	+	++++	+	0	0	0	0	0
5	2/25	E	+	+	0	0	0	0	+
6	2/27	++	++	+	+	0	0	0	0
7	2/28	+	+	0	0	0	0	0	0
8	2/28	+	0	0	0	0	0	0	0
9	3/1	+	+	+	0	0	0	0	0
10	3/1	+	0	0	0	0	0	0	0
11	3/2	++	++	+	0	0	0	0	0
12	3/2	++++	++++	++	+	0	0	0	0
13	3/2	+	+	+	0	0	0	0	0
14	3/3	E	E	0	0	0	0	0	0
15	3/3	0	+	0	0	0	0	0	0
16	3/5	+	E	0	0	0	0	0	0
17	3/5	++++	++++	++++	+	+	+	0	++++
18	3/5	+	+	+	0	0	0	0	0
19	3/6	0	+	+	0	0	0	0	0
20	3/6	E	E	0	0	0	0	0	0
21	3/6	E	E	0	0	0	0	0	0
22	3/6	+	+	+	0	0	0	0	0
23	3/7	+	+++	+	0	0	0	0	0
24	3/7	+	+	+	+	0	0	0	0
25	3/7	E	E	0	0	0	0	0	0
26	3/8	++++	++++	++++	+	0	0	0	0
27	3/8	+	0	+	0	0	0	0	0
28	3/9	+	+	+	+	0	0	0	0
29	3/9	++	⊕	++	⊕	⊕	0	0	0
30	3/12	+	++++	+	0	0	0	+	0
31	3/12	++++	++++	+++	+	+	0	+	+
32	3/22	+	0	+	0	0	0	0	0
33	3/22	+++	+	+	0	0	0	0	++
34	3/23	++++	+++	++	+	0	0	0	++
35	3/24	+++	+++	++	+	+	+	0	++
36	3/27	++	+++	+	0	0	0	0	0
37	3/29	++++	++++	++++	++	+	+	0	++
38	3/30	+++	+++	+++	0	0	0	0	0
39	4/2	++	+++	++	+	0	0	0	0
40	4/2	+	+++	+	0	0	0	0	0
41	4/3	+	0	0	0	0	0	0	0
42	4/4	+++	+++	+	0	0	0	0	0
43	4/5	+	+++	+	0	0	0	0	0
44	4/6	++++	++++	++	0	0	0	0	+
45	4/9	+	0	0	0	0	0	0	0
46	4/10	+	+	+	0	0	0	0	0
47	4/10	++	++	+	+	0	0	0	0
48	4/11	++	+++	+	0	0	0	0	0
49	4/16	++++	+++	++	0	0	0	0	0
50	4/16	++	++	+	0	0	0	0	0

formed in the manner outlined above. The results are given in Tables VII, VIII, IX and X.

The notation used in listing the severity of the reactions is as follows: the wheal was measured in its two longest directions, at right angles to each other, and these numbers were multiplied together. This represented roughly a square area. When the results were from 50 to 100 sq. mm. the reaction was classed as +; from 100 to 200 sq. mm., as ++; from 200 to 300 sq. mm., as +++; from 300 to 400 sq. mm., as ++++; and above 400 sq. mm., as +++++. Thus if a wheal was 10 by 15 mm. the reaction was classed as ++.

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TABLE VIII. RUSSIAN THISTLE

Patient	Date	Control	1st NaCl	2nd NaCl	3rd NaCl	4th NaCl	5th NaCl	1st Alcohol	1st NaOH
1	2/20	+	+	0	0	0	0	0	0
2	2/20	+	+	0	0	0	0	0	0
3	2/22	+	0	0	0	0	0	0	0
4	2/22	+	+	0	+	0	0	0	0
5	2/25	++++	++++	++++	++++	+++	+	0	0
6	2/25	+	+	+	0	0	0	0	0
7	2/27	0	+	+	+	0	0	0	0
8	2/28	+	0	+	0	0	0	0	0
9	2/28	+	+	0	0	0	0	0	0
10	2/28	++	+++	++	0	0	0	0	0
11	2/28	++	++	+	+	0	0	0	0
12	3/1	+	+++	+	0	0	0	0	0
13	3/1	+++	+	+	+	0	0	0	0
14	3/2	+	+	0	0	0	0	0	0
15	3/2	++	++	+	0	0	0	0	0
16	3/2	++	+	+	0	0	0	0	0
17	3/2	+	+++	+	0	0	0	0	0
18	3/3	+++	+++	++	++	+	0	+	++
19	3/3	++	++	+	+	0	0	0	+
20	3/3	+	++	0	0	0	0	0	0
21	3/5	+	+	+	0	0	0	0	0
22	3/5	+	++	+	+	0	0	0	0
23	3/5	++	+	+	0	0	0	0	++
24	3/6	++	++++	++	+	0	0	0	0
25	3/6	++++	++++	++++	++	++	++	0	++++
26	3/6	+	+	+	0	0	0	0	0
27	3/6	+	+	+	+	0	0	0	0
28	3/6	+++	+	+	+	0	0	0	0
29	3/7	++	++	+	+	+	0	0	+++
30	3/7	++++	++++	++++	+	+	0	0	0
31	3/8	++	+++	++	+	0	0	0	0
32	3/8	+++	++++	++	+	0	0	0	+++
33	3/9	+	+	+	0	0	0	0	0
34	3/9	++	++	++	+	0	0	0	0
35	3/12	++++	++++	++++	++	+	0	+	++++
36	3/12	+	+	0	0	0	0	0	0
37	3/16	+	0	0	0	0	0	0	0
38	3/22	++	++	++	0	0	0	0	0
39	3/24	+++	++++	++	+	0	0	0	0
40	3/27	++++	++	++	+	0	0	0	+++
41	3/29	+	++	+	+	0	0	0	0
42	3/29	+++	++++	++	+	0	0	0	0
43	3/30	+	+	0	0	0	0	0	0
44	4/2	++++	++	++	+	0	0	0	+
45	4/2	+	++	+	+	+	+	0	+
46	4/3	++	++++	++	+	0	0	0	++
47	4/4	++++	++++	++	+	0	0	0	0
48	4/5	+++	++++	++	+	0	0	0	+
49	4/6	+++	++	+	+	+	0	0	+++
50	4/9	+	+	+	0	0	0	0	0
51	4/9	+	+	0	0	0	0	0	0
52	4/10	+++	++++	++++	0	0	0	0	0
53	4/10	+	+	0	0	0	0	0	0
54	4/11	+++	++++	++	+	+	+	0	+++
55	4/16	++	++	++	+	0	0	0	0
56	4/16	+	++	+	0	0	0	0	0
57	4/16	++++	++++	++++	++	+	+	0	++

## DISCUSSION OF CLINICAL RESULTS

*Sodium Chloride—Ethyl Alcohol—Sodium Hydroxide Extracts.*—From an inspection of Tables VII, VIII and IX it will be noticed that all the patients who were sensitive to the control glycerosaline extract were likewise positive to the saline extracts and depending on the degree of reaction they reacted to saline extracts 1, 2, 3, et cetera. Very few patients reacted to all five of the saline extracts, one example being timothy

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TABLE IX. SHORT RAGWEED

Patient	Date	Control	1st NaCl	2nd NaCl	3rd NaCl	4th NaCl	5th NaCl	1st Alcohol	1st NaOH
1	2/20	++	+	+	0	0	0	0	0
2	2/21	++	++++	0	0	0	0	0	0
3	2/25	+	+	++	+	0	0	0	0
4	2/25	+++	+	+	0	0	0	0	0
5	2/27	+	+	0	0	0	0	0	0
6	2/28	++++	++++	+++	++	0	0	0	0
7	3/1	++	++	+	0	0	0	0	0
8	3/1	++	++	0	0	0	0	0	0
9	3/5	++	0	+	0	0	0	0	0
10	3/5	+	+	++	+	0	0	0	0
11	3/5	+	+	+	0	0	0	0	0
12	3/7	0	+	+	0	0	0	0	0
13	3/7	+	++	++	+	0	0	0	0
14	3/7	0	+	0	0	0	0	0	+
15	3/7	+	+	0	0	0	0	0	0
16	3/9	++++	++++	+++	0	0	0	0	++
17	3/12	++++	++++	++	+	0	0	0	+
18	3/24	+	+	0	0	0	0	0	0
19	3/27	+	++	++	+	0	0	0	0
20	3/29	0	+	0	0	0	0	0	0
21	3/30	+	+	0	0	0	0	0	0
22	4/2	++++	++++	++	++	0	0	0	0
23	4/2	+	+	0	0	0	0	0	0
24	4/3	+	+	+	0	0	0	0	0
25	4/6	0	+	0	0	0	0	0	0
26	4/10	+	+	++	0	0	0	0	0
27	4/10	++++	++++	++++	++	+	0	0	0
28	4/11	+	+	+	0	0	0	0	0
29	4/16	++	++	+	+	+	0	0	0
30	4/16	+	+	+	0	0	0	0	+
31	4/17	+	++	++	++	+	0	0	0

patient No. 17. The individuals who are interesting in these tables are those who, for example, reacted to the first, second, and third sodium chloride extracts, were negative to extracts four and five, also negative to the first alcohol extract but positive to the first of the sodium hydroxide extracts. This would indicate that some of the patients were sensitive not only to the antigen or antigens which were extracted with sodium chloride but also to some antigen or antigens which were extracted with sodium hydroxide. This is the case with timothy patients Nos. 2, 5, 30 and 31. Patients Nos. 17 and 37 are also interesting because these patients are very sensitive to timothy. They reacted positive to sodium chloride extracts 1, 2, 3, 4, and 5, with decreasing intensity, however. They were negative to the alcohol extract and then very positive to the sodium hydroxide extract. This would seem to indicate that an additional skin-exciting substance was being extracted by the sodium hydroxide solution. An inspection of Tables VII, VIII and IX will also reveal that approximately 18 per cent of the timothy-sensitive patients were positive to the sodium hydroxide extractable chemical or chemicals. Likewise 25 per cent of the Russian thistle-sensitive and 13 per cent of the ragweed-sensitive patients reacted in the same manner. The low percentage in the case of the ragweed-sensitive patients can easily be explained. For only those patients react with the sodium hydroxide extract who are quite sensitive and in the Pacific Northwest very few have severe allergy due to ragweed.



TABLE X

Patient	Date	RAGWLED					TIMOTHY					RUSSIAN THISTLE				
		Control	First Water Extract	Third Water Extract	Fifth Water Extract	First Saline Extract	Control	First Water Extract	Third Water Extract	Fifth Water Extract	First Saline Extract	Control	First Water Extract	Third Water Extract	Fifth Water Extract	First Saline Extract
1	4/27	0	0	0	0	0	++	++	0	0	0	++	++	0	0	0
2	4/27	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
3	5/1	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
4	5/4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
5	5/4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
6	5/4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
7	5/4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
8	5/8	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
9	5/8	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
10	5/8	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
11	5/8	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
12	5/11	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
13	5/11	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
14	5/11	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
15	5/12	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
16	5/18	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
17	5/18	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
18	5/18	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
19	5/18	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++

*Water and Sodium Chloride Extracts.*—Table X, which shows the reaction of patients to the water-extractable chemical or chemicals also indicated some interesting facts. First, it will be noticed that a high percentage of individuals who are sensitive to the three tested pollens are also sensitive to a chemical or chemicals which are extracted by sodium chloride after five successive aqueous extractions have removed almost all the water-soluble nitrogen compounds. If this nitrogenous substance or substances which are being extracted by the sodium chloride is of proteinoid character then it would be classed as a globulin, i. e., a protein which is insoluble in water but soluble in sodium chloride solutions. This is again another indication that the skin-exciting chemical is of proteinoid character. The high percentage of patients who react to these substances is remarkable. In the case of ragweed, of the seventeen tested, ten were sensitive to one of the extracts and eight of these reacted to the sodium chloride-extractable chemical or chemicals, and eight to the water-extractable chemical or chemicals. It is also interesting to note that one individual (No. 2) was sensitive to the sodium chloride extract but was not sensitive to the water extract. Nothing of course can be argued from a single case. Of the fourteen timothy-sensitive persons, seven gave wheals with the sodium chloride extract and thirteen reacted to the water extract. Of the fifteen individuals who were Russian thistle sensitive, eleven reacted to the sodium chloride extract and all to the water extract. These percentages, viz., 80 per cent, 50 per cent and 73 per cent, indicate that a large number of hay fever sufferers are sensitive to at least two classes of substances both of which, however, can be extracted from the pollen by sodium chloride solutions. It is also probable that some patients are sensitive to three classes of compounds. Stull, Cooke and Chobot<sup>27</sup> claim that the globulin fraction has no activity, this being at direct variance with the results listed above.

Finally, we have an indication that the protein nitrogen unit and the total nitrogen unit do not give an adequate measure of the potency of an extract. In the case of those individuals who are sensitive to both the water-extractable chemicals and the sodium chloride-extractable chemicals, if we were to judge the potency of an extract on a protein nitrogen unit basis, then it would be logical to suppose that the water extract was as potent in treating those cases as the sodium chloride extract, provided that both were diluted to the same protein nitrogen content or the same total nitrogen content. Yet such would not be the case because the chemical which is extracted by the sodium chloride would be absent from the water extract and yet the protein nitrogen unit content would be the same. Consequently, the presence of protein nitrogen or total nitrogen in an extract from a pollen does not give an absolute measure of potency.

For a specific pollen, however, which has been extracted by a specific extracting medium, the same argument does not hold. Then there may be a definite relationship between the protein nitrogen content or the total

nitrogen content and the potency of the extract. But the mere use of the protein nitrogen unit or the total nitrogen unit without further qualification is not a sufficient norm in standardization. This is very probably the basis for the difficulty sometimes encountered in changing from the extract of one individual to that of another who does not use the same extracting medium. The protein nitrogen content or total nitrogen content may be diluted to the same strength and yet their relative clinical strength may be different.

*The Alcohol Extracts*—No evidence could be found for the existence of an alcohol-soluble antigen. The very few instances in which reaction took place could be ascribed to other causes, so no conclusions are claimed.

The results which were found in this investigation substantiate many isolated instances which have been recorded in the literature. Thus the existence of a water-soluble antigen in ragweed, as claimed by Caulfield, Cohen, and Eadie<sup>3</sup> is confirmed. The results of Johnson and Rappaport<sup>9</sup> also agreed with the results here obtained. They reported two fractions in ragweed, an albumin and a globulin fraction. Stull, Cook, and Chobot<sup>28</sup> found one active substance in timothy to be an albumin (water soluble). Again the results here obtained confirm the findings. Caulfield, et al.<sup>4</sup> show that there must be more than one antigen in ragweed while Stull, Sherman and Wing<sup>25</sup> show the existence of three antigens in ragweed, which results are here confirmed. Stull, Sherman, and Hampton<sup>29</sup> go a step further and say that the water-soluble fraction is made up of two antigens and if this be the case there are at least four chemicals in ragweed which can cause skin reactions.

The next work which the authors will undertake will be a further fractionation of the extracts so far obtained with the objective of determining whether these fractions contain one or more antigens.

#### SUMMARY

1. Of the nitrogen extracted from timothy, Russian thistle and ragweed approximately two-thirds of it is in the form of protein nitrogen (phosphotungstic acid precipitable).
2. Water is a better extracting medium for nitrogen in the case of timothy, Russian thistle and ragweed than a 10 per cent solution of sodium chloride.
3. Water is more efficient in removing protein nitrogen from timothy and ragweed than a 10 per cent solution of sodium chloride. This is not true for Russian thistle.
4. At least three antigens are present in ragweed, timothy and Russian thistle, a water-soluble substance or substances, a saline-soluble substance or substances and an alkali-soluble substance or substances.
5. In view of the fact that extracting media vary and also because there is no single protein or proteinoid substance extracted neither the protein

nitrogen unit nor the total nitrogen unit gives an adequate measure of the potency of that extract.

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# FATIGUE AND WEAKNESS OF ALLERGIC ORIGIN (ALLERGIC TOXEMIA) TO BE DIFFERENTIATED FROM "NERVOUS FATIGUE" OR NEURASTHENIA

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ALLAN<sup>1,2</sup> recently reported an analysis of 300 cases in which examination was requested because of the complaint of fatigue, weakness or weak spells. Physical disorders were found to explain the complaint in only 20 per cent, the remaining 80 per cent were allegedly the result of a "nervous condition"; "benign nervousness" in the majority in distinction to a smaller group having true neuroses.

Allan's apriorism that "nervousness" explains all fatigue and weakness otherwise unexplained warrants careful scrutiny. This view not only diagnoses psychosomatic disease by exclusion of physical disorders but also overlooks the etiologic roles of yet to be discovered causes of fatigue and weakness or of known causes not associated with abnormalities of the physical examination, x-ray and other routine laboratory procedures. In the latter connection, Allan's report neglected to mention the fatigue and weakness of allergic origin.

A review of so-called allergic toxemia or allergic fatigue is particularly appropriate in view of the fact that fatigue from this cause and the fatigue alleged to result from neuropsychiatric disturbances<sup>1,2,9</sup> have many common features. Furthermore, until very recently the subject of fatigue in relation to chronic allergy has been discussed under the title of allergic toxemia or has been mentioned as parts of other communications in the field of allergy. The connotation of weakness or fatigue due to an allergic reaction has not been expressed as such in the titles of these presentations, with the result that this factor might readily be overlooked by one collecting a bibliography on the subject of fatigue. The frequency of this manifestation and the fact that it is usually misdiagnosed offer additional incentive to review the subject.

We are indebted to Rowe<sup>18,19,20</sup> for the first clear description of the fatigue syndrome occurring as a result of food allergy. In 1928 Rowe referred to this condition as allergic toxemia and stated that this toxemia produces drowsiness, mental confusion, slowness of thought, lack of initiative and ambition, irritability, despondency, fatigue, weakness bodily aching and a feeling of being poisoned. He pointed out that these symptoms commonly occur in association with other allergic reactions particularly with headaches, gastro-intestinal and nasal symptoms of allergic origin. Rowe<sup>21,22</sup> emphasized the occurrence of these symptoms in adult life, the fact that they occurred more commonly in women than in men and that as a rule patients with these complaints did not suspect the diet as an etiologic factor.

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Moreno<sup>18</sup> in 1940 confirmed Rowe's observations and stressed the importance of "toxemia alergica" in interfering with the daily activity of individuals in responsible positions of society as a result of alterations in the individual's attention, memory, initiative and intelligence.

One may find scattered references to the subject of unexplained fatigue and weakness in the allergic individual prior to these descriptions of allergic toxemia. Salter<sup>25</sup> in 1882 described the precursory symptoms of asthma by stating: . . . "The patient will feel himself very drowsy and sleepy, will be unable to hold his head up or keep his eyes open, and that without having undergone any particular fatigue or done anything that could account for it." Salter cited Sir John Floyer, who had written in the sixteenth century: "There appears a great dulness and fulness in the head with a slight headache and great sleepiness before the fit (asthma)."

Laroche, Richet and Saint Girons<sup>7</sup> in 1919 noted the presence of fatigue in allergic children and were the first to call attention to the fact that it was related to food allergy.

In 1923 Duke<sup>4</sup> commented on weakness and nervousness as symptoms of food allergy and in 1925<sup>5</sup> referred to asthenia as a common reaction which may vary from a slight feeling of weakness to asthenia so profound as to prevent the patient from lifting a hand. He stated that the symptoms in less severe grade were relatively common in patients with mild general allergy. Kahn<sup>6</sup> called attention to the relationship of fatigue and pollinosis in 1927. Vaughan<sup>27</sup> mentioned the "droopy, loggy, 'no count' feeling" resulting from the ingestion of an allergenic food. Similar symptoms in patients with chronic food allergy have been observed by others during the past decade.

Since 1942 we<sup>13</sup> have noticed that several young individuals under study for allergic disorders had previously been suspected of having infectious mononucleosis. The latter diagnosis had been regarded as a possible explanation for the weakness, lassitude and general malaise exhibited by these patients. In some instances glandular fever had been suggested by the presence of recurrent cervical lymphadenopathy or the finding of atypical lymphocytes in the peripheral blood. However, the diagnosis of infectious mononucleosis was only rarely confirmed by the findings of a positive heterophile antibody determination.

These observations prompted us<sup>14</sup> to survey the members of the junior and senior classes of the University of Michigan Nursing School, inquiring specifically into the history of allergic disease and the occurrence of "fatigue and weakness unrelieved by rest." The incidence of a past history of allergy in 83 or 59.2 per cent of the group of 140 agreed with the results of previous surveys. However, 51.8 per cent of the group with a past history of allergic disease had been subject to periods of "fatigue unrelieved by rest" against only 5.3 per cent of the group with negative allergy histories. Furthermore, infectious mononucleosis, the symptomatology of which is characterized by profound fatigue and weakness,

had been suspected in 31.5 per cent of the cases with positive allergy histories against 3.6 per cent of those with negative histories; it was actually diagnosed on the basis of an unequivocally positive heterophile antibody titer in only one case of each group. This survey established the earlier impression of the prevalence of unexplained fatigue as a manifestation of the uncontrolled allergic reaction.

Weakness and fatigue as the result of food allergy most commonly begin as intermittent episodes in association with some other allergic manifestation. As mentioned by Rowe, the syndrome most commonly accompanies a gastro-intestinal allergic response, allergic headaches or nasal allergy. The association with episodes of allergic headache or migraine is striking. Rinkel<sup>16</sup> recently re-emphasized this association by stating that one must consider tiredness as a precursor of headaches. He pointed out that a food which is taken every three or four days and produces only tiredness will, if used repeatedly, produce headache. In the individual episode the fatigue may precede the onset of the headache or develop anytime during the attack but when associated it almost invariably persists for several hours after the headache has subsided. There often is a similar relationship of fatigue with attacks of gastro-intestinal allergy. As the incidence of headaches or gastro-intestinal episodes increases, the fatigue is apt to persist between attacks and not infrequently becomes the patient's major complaint. In respect to nasal allergy the fatigue is not usually associated with the transitory attack of rhinitis and only becomes a troublesome feature of the chronic case. There remain, however, marked variations in the incidence and severity of the fatigue syndrome in different allergic individuals.

Commonly the onset of fatigue and weakness is so insidious that the patient is not fully aware of his current debility; he often appreciates the severity and incapacitating nature of his former symptoms after they have been relieved. As a result, this manifestation of allergy is commonly overlooked in taking routine allergy histories, particularly if one ascribes to the habit of checking history forms. If adequate inquiries are made in reference to it, allergic fatigue is found to be present to variable degrees in a relatively large percentage of patients who submit themselves for an allergic investigation. Although the fatigue syndrome may be associated with either intermittent or chronic and persistent allergic manifestations, the chronic cases present the major problem in differentiating fatigue of allergic origin and other causes of malaise and weakness. This is the type of patient who is apt to list his fatigue as his major complaint.

The fatigue related to chronic food allergy is usually more pronounced in the early morning hours and often, although by no means invariably, decreases as the day progresses. These individuals commonly remark that they are more tired when they arise in the morning than when they went to bed in spite of obtaining the customary eight hours of sound sleep. Sleeping from ten to sixteen hours for several nights in succession, or

remaining in bed over the weekend in an effort to overcome the fatigue does not afford relief. This is so characteristic and so unlike the fatigue from physical exertion that one may designate this condition as "fatigue unrelieved by a formerly adequate or excessive amount of rest."

It should be mentioned at this point that Allan<sup>1,2</sup> and Portis and Zitman<sup>9</sup> also characterize the fatigue and weakness arising from a nervous state as greater in the morning and wearing off during the day. Allan further listed as another pathognomonic feature the fact that the fatigue was variable from day to day, without change in activity to account for the difference. This description is equally pertinent in reference to the fatigue of allergic origin.

Unlike the fatigue occurring as the result of physical exercise, individuals with a chronic uncontrolled allergic reaction characteristically have a basal or pre-exertion fatigue or weakness which often requires a distinct effort or "push" to start the daily work. Some complain of having to push themselves all day. In addition, these individuals seem to tire more easily as the result of exertion. The lack of the desire to work and the loss of the previous initiative and ambition have been emphasized by both Rowe and Moreno. Some actually complain of being too tired to move, yet resting does not relieve them!

Mental sluggishness, inability to concentrate or maintain attention are more common in some individuals than others. These symptoms are often observed more clearly when the fatigue syndrome is present in intermittent attacks. At this stage the office worker is inclined to save up tasks requiring concentration and mental alertness for his better days. When present intermittently the patient is usually aware of his bouts of fuzzy thinking and lack of efficiency. With persistence of symptoms he may lose sight of the contrast with his previous normal self and not uncommonly degenerates to a level of lowered efficiency.

Abnormalities of memory often characterize the allergic individual with the fatigue syndrome. The inability to remember details or to carry out instructions is a frequent handicap. This is particularly troublesome when dealing with some situation slightly different from the daily routine.

Irritability or crankiness is often noted by members of the family or co-workers, in contrast to the behavior of these individuals prior to the onset of their allergic manifestations. The patient commonly complains of being tense and annoyed by small points ordinarily taken in stride. This reaction is often marked in children and may be observed in them with less interference than in adults. Small children often become sullen, lose their desire to play and frequently react negatively to suggestions. Such periodic bouts of behavior in otherwise well-adjusted children are perplexing to both parents and teachers.

The fatigue in these cases has been described as unrelieved by either a formerly adequate or excessive amount of rest. There is some question whether these individuals, subject to toxic allergic reactions actually obtain



undisturbed rest or, stated differently, whether their sleep, although adequate quantitatively, may be inferior qualitatively. There is no satisfactory method to use in determining this point. The observation remains that some adults with this syndrome complain of restlessness at night, a tendency to awaken several times or to have frequently disturbing dreams in contrast to less disturbed sleep after the institution of allergic control. Other adults with identical symptoms obtain normal, undisturbed sleep as far as can be determined. The apparent necessity of taking sedatives for sleeping and the non-necessity for the same after dietary regulation are sometimes observed. This restlessness is often more clearly seen in children although the individual child may not be subject to any manifestation of allergy associated with obstruction to breathing or pruritus. These children not infrequently cry out during the night or are unusually cross when for any reason they are awakened. Quite obviously other factors may cause a similar reaction but the association in this connection should be noted.

Various degrees of mental depression may exist; this ranges from a mild depression in spirits to the point that an individual may shun association with others. Despondency and melancholia have been observed in a few cases to the degree that the patient or members of the family inquire about the possibilities of mental illness.

There are certain other constitutional manifestations at times observed in the patient with the fatigue syndrome as a result of chronic allergic reactions. These include localized or generalized muscle aching and soreness or drawing sensations in groups of muscles, particularly those of the posterior neck, back and the hamstring muscles of the thighs. The complaint of backache with localization of the discomfort to either the cervical, thoracic or lumbar region has been noted. Although sensory changes are not usually observed, one should recall the peculiar paresthesias often associated with the migraine type of headache.

There is evidence that the lymphoid tissue participates in the allergic reaction, as seen most clearly in the lymphadenopathy associated with serum sickness. As previously mentioned, one may obtain a history of recurrent bouts of unexplained cervical lymphadenopathy more commonly in allergic than non-allergic individuals. The common association of enlarged, edematous tonsils and tender, enlarged cervical lymph glands in the absence of any conclusive evidence of infection, is often observed in the allergic child. The presence of hypertrophied islands of post-pharyngeal lymphoid tissue is another feature of the general picture of lymphoid hyperplasia observed in allergic children and young adults and is not infrequently accompanied by the fatigue syndrome. The presence of atypical lymphocytes in the peripheral blood of patients with histories suggestive of infectious mononucleosis but without the positive heterophile antibody titer usually associated with that disease, has also been noted.

A tendency for edema is manifested by some food allergic individuals

and sometimes accompanies the fatigue syndrome. This is usually observed most clearly in the region of the eyes; it is characterized by puffiness of both lids and fulness and discoloration of the infraorbital areas. Variations in the degree of puffiness of the eyes are seen most clearly in the allergic individual under daily observation as, for instance, by a member of one's family. The alert and observing mother often associates the appearance of the eyes with the presence of allergic symptoms; sometimes the eye manifestations are the only objective evidence of current allergic intolerance. Although the so-called "circles under the eyes" may be the result of other causes, they have been observed to disappear in allergic individuals with the institution of dietary management and to reappear with experimentally or accidentally induced allergic reactions.

The tendency toward otherwise unexplained febrile reactions, tachycardia, chilliness or perspiration has previously been noted in the allergic individual in association with food sensitization. Tachycardia, chilliness and sweating are not infrequently observed in connection with the transitory reproduction of weakness and tiredness following test feeding of allergenic foods,<sup>15,17</sup> or the cumulative re-addition to the diet of an offending food previously avoided for a few days.

The symptoms characteristic of the fatigue syndrome as the result of food allergy may occur at any age, in keeping with the fact that the manifestations of food allergy are not limited to any age group. Although contributing and complicating factors capable of producing fatigue, weakness or the other symptoms mentioned are more apt to co-exist in adults of middle age or past, the fact remains that clear-cut instances of allergic fatigue may be observed in this age group.

The recognition of offending foods depends upon the same diagnostic methods useful in detecting specific ingestants causing other allergic manifestations. A detailed history is an important aid in the diagnosis. Basic elimination diets remain the most generally useful diagnostic procedures available to the profession. The standardized elimination diets as outlined in detail by Rowe<sup>23</sup> are recommended. His cereal-free elimination diet 1, 2, and 3, or the fruit-free, cereal-free elimination diet 1, 2 and 3 are suggested as initial diagnostic plans; minor variations may be made from these in view of specific information obtained in the food history. Follow-up diagnostic diets are prescribed as appear to be indicated in the individual case.

Dietary plans based upon test-feeding procedures as outlined by Rinkel<sup>17</sup> and by us,<sup>15</sup> or by Squier and Madison,<sup>26</sup> are advantageous in that test-negative foods may be included in the initial diet. This usually permits the more complete elimination of other potential offenders and often serves to shorten the diagnostic process. In this respect the individual feeding test<sup>15,17</sup> is preferred over Squier and Madison's modification of the leukopenic index,<sup>26</sup> in view of technical difficulties of the latter method.<sup>11</sup> The feeding test with coincidental pulse measurement as used by Coca<sup>3</sup>

appears to be helpful in certain cases. The author has not had sufficient experience with this method to appreciate fully its apparent limitations.

During the diagnostic period it is essential that specific foods be eliminated completely and that the patient adhere rigidly to the outlined plan. This is facilitated by supplying suggested menus, specific recipes and checking a food diary which is kept by the patient during the interval.

Neither cutaneous nor intracutaneous tests with foods are essential; they often are more misleading than helpful, due to the frequency of false positive and false negative reactions. The fallibility of skin tests with ingestants, as stressed by Rowe, cannot be overemphasized in view of the vogue in some quarters to assign a literal and quantitative interpretation to such findings. One cannot rely solely upon positive skin tests to detect specific offenders or, of even greater importance, upon negative skin reactions to rule out the possibility of food allergy.

The foods most commonly responsible for the manifestations of chronic fatigue and weakness are those included in the diet with greatest frequency. Although sensitivity to wheat, corn, milk and eggs is encountered most commonly, any food eaten regularly may be an offender. The patient often develops a delayed and cumulative reaction from the oft-repeated ingestion of one or several allergenic foods; this mechanism, described as masked food allergy by Rinkel,<sup>16</sup> appears to be particularly effective in producing the various manifestations of the fatigue syndrome. Under such circumstances the patient usually has no conception that the diet is in any way related to the genesis or the perpetuation of the fatigue and, if suspected, the most intelligent individual is usually unable to detect the specific dietary offenders. In fact, not infrequently, the sufferer claims that an improvement in the fatigue is noted after a meal containing a regularly ingested masked food allergen. The early morning accentuation of the fatigue is typical of the masked or latent food reaction.

This chain of events must be interrupted in order to demonstrate the relationship of specific foods to the manifestations of fatigue or other allergic symptoms. With specific avoidance of offenders, the fatigue and weakness characteristically begin to improve on the third or fourth day although sometimes longer periods are required for improvement. Failure to respond on the initial diet does not necessarily mean that a food mechanism is not responsible; this may be due to several causes such as the retention in the diet of one or more allergens, failure to eliminate specific foods completely or possibly the co-existence of complicating inhalant sensitivity. In all instances inhalant sensitivity should be brought under control before attempting to interpret the results of dietary changes.

After the complete avoidance of an incriminated food for four or five days with consequent improvement in symptoms, one often is able to reproduce or accentuate the fatigue and weakness by feeding the given food fasting. The ability of the individual food test, which is performed under

these circumstances, to indicate specific sensitivity by means of precipitated symptoms or a post-prandial leukopenia is an advantage of that technique. When a given food has been avoided for longer periods it often is necessary to ingest it repeatedly for several days in order to precipitate symptoms.

The fatigue of allergic origin is often overlooked or misunderstood because the allergic manifestations most frequently associated, namely, the allergic headache, abdominal and nasal allergy, are commonly not diagnosed correctly from the standpoint of their etiology. For instance, the fundamental allergic origin of the migraine syndrome is not yet fully appreciated by the profession and there is reason to believe that gastrointestinal allergy is not diagnosed with a frequency comparable to its incidence, due to failure to use diet trial freely. The absence of positive findings on physical examination and laboratory studies characterizes both conditions. Furthermore, confusion in the differential diagnosis of allergic rhinitis still exists, many cases either being overlooked or alleged to be the result of common colds or sinus infection. Far advanced allergic rhinitis, bronchial asthma, atopic dermatitis or urticaria are more readily detected on physical examination. Although the characteristic fatigue and related symptoms may be associated with these allergic expressions, the picture is often distorted by interference in obtaining sleep as the result of obstruction to breathing or pruritus. However, there is suspicion that the so-called debility in bronchial asthma recently described by Rackemann<sup>10</sup> is an identical symptom.

Cases of unexplained fatigue of the type described may be observed in individuals who, at the time seen or in their past histories, fail to show any evidence of other allergic manifestations. This was brought out by Rowe in his initial reference to the subject; he stated that the effects of food allergy seem to disturb the whole body in these patients and may not produce any of the typical manifestations of abdominal allergy, urticaria, angioneurotic edema, eczema, migraine, bronchial asthma, rhinitis, or other allergic disturbances of the nervous system or genito-urinary system. Rinkel<sup>16</sup> also claimed that many patients have toxic symptoms from foods but do not exhibit classical allergic syndromes. The author is inclined to agree with Rowe<sup>24</sup>, who states: "I use my elimination diets for the study of possible food allergy in all patients suffering from fatigue which is not obviously due to some other cause."

The underlying physiological mechanism responsible for the fatigue and weakness in these cases is not understood.

As a rule these patients do not respond to extended rest periods or vacations either at home or away from home. They fail to be relieved by thyroid, estrogenic or vitamin therapy. The response to the elimination of specific allergens is usually striking. The relief of the fatigue by trial diet is often the first indication of the allergic etiology of related symptoms, a course of events illustrated by the response to diagnostic elimination diets

in a recently reported case of fatigue associated with allergic headache.<sup>12</sup> Other times the concurrent allergic manifestation may be improved by dietary control and the fatigue and weakness will gradually subside during a period of several weeks. This type of response suggests that the food or inhalant sensitivity has not been worked out completely or that contributing non-allergic factors are also operating.

Before considering the differential diagnosis of allergic versus "nervous" fatigue it is essential that the medical study, including the history, physical examination and diagnostic laboratory procedures should have been performed with the aim of detecting other causes of fatigue. As listed by Allan<sup>1,2</sup>, these include chronic infections, metabolic disorders with particular emphasis on hypothyroidism and diabetes, neurological disorders including myasthenia and narcolepsy, heart disease, anemia, dietary deficiencies and malignancy. In some instances, such as hypothyroidism and nutritional deficiencies, a trial period of thyroid medication or correction of the diet by means of protein, vitamin or mineral supplements is an essential part of diagnostic studies. Obviously, chronic exhaustion as a result of overwork or inadequate sleep should be evaluated.

It must not be assumed that the existence of clinical allergy and nervous manifestations are mutually exclusive, as any chronic illness may be complicated by a psychogenic component. The differential diagnosis between fatigue and weakness of allergic or nervous origin is rendered difficult by the fact that the two conditions apparently have several descriptive features in common. In cases where both factors apparently exist, the significance of the nervous element is more accurately judged after an attempt has been made to diagnose and control the allergy. This attempt must include some type of trial diet. If physicians used freely the available diagnostic methods for the specific detection of food allergens, many cases of such disabling allergic manifestations as the fatigue syndrome described, headaches or gastro-intestinal symptoms, would be more correctly appraised. It is a truism that physicians steeped in the traditional aspects of medicine who do not possess a working concept of clinical allergy are inclined to emphasize apparent psychogenic factors in the genesis of these conditions. The current tendency to assume that psychosomatic disease is responsible for symptoms of the type described, unexplained as a result of the traditional medical investigation, stigmatizes many unfortunate allergic individuals with a diagnosis of psychoneurosis, or even psychosis, and leaves them to their own resources in coping with their disabling symptoms. The majority of allergic individuals with the fatigue syndrome as a major complaint eventually seen by the author have been previously diagnosed as "neurotics."

No attempt has been made in this presentation to review the subject of fatigue and weakness as possible neuropsychiatric manifestations. An effort is made to re-emphasize the clinical picture of fatigue, weakness and related symptoms as expressions of uncontrolled allergy, pointing out par-

ticularly that these manifestations commonly occur in the absence of abnormalities disclosed by the routine physical examinations and laboratory procedures. The mere absence of positive findings in this respect does not justify the frequently made assumption that "nervousness" is therefore operating.

The following cases are illustrative of the toxic manifestations of food sensitization:

*Case 1.*—J. R., a businessman, aged forty-two, developed intermittent nasal stuffiness and postnasal dripping six months following a tonsillectomy in 1930. Although the rhinitis was present perennially there was an accentuation of symptoms with sudden changes in temperature or immediately before storms. He had also been subject to periodic frontal headaches beginning in 1930; these commonly occurred between one and two hours after the evening meal and persisted for six to twelve hours. The headaches were invariably associated with and followed by marked lassitude and fatigue. As time passed and the headaches became more frequent he developed chronic fatigue and weakness which were not relieved by the amount of sleep that formerly caused him to feel rested. When first seen in 1943 his major complaint was fatigue and a lack of initiative and ambition in contrast to his former self.

He had avoided chocolate for several months after learning that it invariably produced a stuffy nose and headache 30 minutes following ingestion. He had been accustomed to drinking a quart of milk daily and beef had been the principal meat of his diet.

His physical examination was negative except for moderate pallor and thickening of the nasal mucosa. Routine laboratory procedures, including blood counts, urine examination and a chest x-ray were negative. A smear of the nasal secretions revealed many eosinophiles.

He was placed on a diagnostic elimination diet avoiding wheat, milk, eggs, coffee, citrus fruit, legumes, chocolate, nuts, condiments and all meats except lamb. The fruits and vegetables were limited to the members of a few botanical families. Complete relief of nasal symptoms, lassitude and headaches resulted. The avoided foods were then returned to the diet cumulatively and tolerated with the exception of beef and milk. On the third day of beef he developed a severe headache lasting ten hours. Another headache occurred one-half hour after the fourth consecutive meal containing a glass of milk. With the continuation of milk he had another headache on the third day. He was definitely more tired and listless during the periods of taking cumulative doses of these foods. With the complete avoidance of chocolate, beef and milk all symptoms again subsided. A month later a headache was precipitated by drinking a single glass of milk. With diet control he remained symptom-free for six months. In the past year milk has been tolerated in cooking and beef has been used once a week without trouble. The relief of symptoms, including fatigue, coincided with improvement in the appearance of the nasal mucous membranes.

*Case 2.*—E. B., an accountant, aged fifty-five, developed gnawing, midepigastria abdominal pain, belching, nervousness and "jitteriness" in attacks two to three hours after certain meals, beginning in 1938. Gastro-intestinal x-ray studies on three different occasions had been negative. At first his symptoms were cyclic and a few times seemed to respond to ulcer management. In mid-1944 he developed periodic attacks of frontal headache associated with scotomata and photophobia; during the more severe attacks he had profuse sweating and vomiting. He complained of extreme fatigue, "dopiness," and sluggishness during and following each bout of head pain. As the incidence of headaches increased his weakness and fatigue became

continuous and of sufficient severity to interfere with his efficiency and accuracy as an accountant. The abdominal symptoms also became more continuous, were present principally at night and were associated with attacks of perspiration early each morning. There had also been an occasional attack of unexplained diarrhea.

Although he suspected no particular food causing distress, he was tested by individual feeding technique<sup>17</sup> with four major foods. Test feedings with wheat and potato resulted in compatible blood responses and were not associated with an accentuation of symptoms. He developed a post-prandial leukopenia following the trial ingestion of both milk and eggs, with severe headaches lasting twenty-four hours. A suggestion of beef sensitivity was obtained from food diary evidence. On a diet eliminating eggs, beef and milk he has been relieved of fatigue with its associated weakness, night sweats and nervousness, violent headaches and chronic gastro-intestinal symptoms. With the elimination of the major offenders he has been able to detect additional intolerance to rhubarb and buckwheat.

*Case 3.*—P. J., a medical technician, aged twenty-four, developed perennial nocturnal rhinorrhea at the age of fourteen, which later became associated with intermittent periods of nasal obstruction. At the age of twenty she began to have frontal headaches associated with anorexia and unusual tiredness. Her bowel habits had been normal until June, 1943, at which time she began having abdominal cramps followed by diarrhea after certain meals. The gastro-intestinal symptoms gradually became more constant and for several months she passed between five and eight liquid stools daily; these contained strings of mucus but no blood. Repeated physical examinations, sigmoidoscopy and x-ray studies failed to reveal the cause of the colitis. A persistent degree of fatigue and lassitude, accentuated in the mornings and unrelieved by excessive rest, was a major symptom.

Eggs had previously been suspected of causing headaches, nausea and vomiting and had been avoided for five years. The results of skin testing with inhalants were negative. Wheat was eliminated four days prior to test feeding, at the end of which period the bowel movements had returned to normal for the first time in several months. An individual feeding test with wheat was associated with a diagnostic leukopenia, marked chilliness, and a frontal headache beginning fifteen minutes after ingestion. These symptoms were accentuated by a second feeding an hour after the first and were associated with profound weakness and fatigue for the remainder of the day. Abdominal cramps began four hours after the test and the following morning she passed two liquid stools for the first time in two days.

Upon the observation that lettuce had been followed by a headache after wheat had been eliminated, it was avoided for four days and tested on the fifth. In the presence of a diagnostic leukopenia she developed chilliness at thirty minutes and a severe frontal headache fifty minutes following ingestion. She had a recurrence of liquid stools the following morning; residual fatigue persisted for 24 hours.

With the avoidance of wheat, lettuce and nuts she has remained entirely free of fatigue, headache and the manifestations of nasal and abdominal allergy.

*Case 4.*—L. M., a contractor, aged thirty, developed perennial nasal stuffiness and rhinorrhea in 1928. His symptoms were not troublesome and he was unaware of unusual fatigue until entering the Army. There he was unable to keep up with others in his unit because of unexplained weakness and ease of fatigue. He was finally discharged from the service. His morning exhaustion and weakness continued in spite of obtaining eleven hours of sleep nightly. He found it exceedingly difficult to remain attentive. He also complained of inability to remember. In addition, he developed mild frontal headaches associated with dizziness, occurring on the average of two to three times weekly; these might be precipitated either by drinking beer or eating peanuts.

An allergic study in early 1944 revealed positive skin tests to house dust and

feathers, although he was not aware of inhalant intolerance and his symptoms were not relieved by a program of specific avoidance.

Following this he was placed on a diagnostic elimination diet with avoidance of all cereals, milk, eggs and legumes. He noticed improvement in his fatigue on the fourth day of the diet and felt good on the ninth. The cumulative addition of beans produced a headache on the second day of their ingestion. All other foods except legumes and wheat were tolerated upon cumulative addition to the diet. Repeated attempts to eat wheat or legumes were followed by the precipitation of a headache, and if they were used for more than a few meals the previous fatigue syndrome was reproduced. He has had complete relief of symptoms with avoidance of wheat, beer, peas, beans and peanuts.

*Case 5.*—R. R., a farmer, aged twenty-eight, had been subject to urticaria following the ingestion of beer since 1933, rhinitis and coughing after exposure to thresher dust since 1934 and nocturnal coughing beginning in 1938. The last-named was completely relieved by a program of feather avoidance. In 1940 an immediate type of serum sickness occurred after receiving a second dose of horse serum. Within a few hours he developed flushing of his face, intense headache, marked weakness, vomiting and a temperature elevation to 105.0 degrees F. which was followed by generalized urticaria. He remained extremely weak and was unable to work for several weeks.

In late 1943 he developed progressive nasal stuffiness, persistent fatigue and profuse night sweating following a common cold. Because his fatigue and weakness were so marked that he was unable to continue with his farm work, and because his nasal symptoms were accentuated in the barn, he sold his farm and for several weeks avoided all farm exposures. In spite of a regulated program of inhalant avoidance his weakness and profuse perspiration continued. Any exertion accentuated his symptoms and made him dyspneic although repeated examinations failed to reveal any evidence suggesting bronchial asthma or a cardiac abnormality. The fatigue was not relieved by avoiding exertion or by obtaining excessive amounts of rest, and at this stage it was his sole complaint.

He showed positive skin tests to rusts, smuts, and feathers, but house dust (Endo) and other inhalants were negative both cutaneously and intracutaneously. In view of his excessive intake of wheat (8-10 slices of bread and 6-10 cookies daily), the history of beer causing urticaria and a positive ingestion test to wheat when checked by the technique of Squier and Madison<sup>26</sup> in 1940, he was placed on a wheat-free diet. Toward the end of the second day of wheat avoidance he began to feel better generally. A striking improvement of the fatigue and a cessation of the perspiration had occurred by the fourth day. Within a week he was working ten to twelve hours a day for the first time in four months; his previous fatigue, lassitude, dyspnea, sweating, and nasal symptoms were absent.

A month later an individual feeding test with wheat, for which he was prepared by the ingestion of a single meal five days prior to test feeding, revealed a typical post-prandial leukopenia and was followed by mild nasal stuffiness and shortness of breath beginning one-half hour after the second dose. Fatigue or weakness did not develop. Wheat was then forced in the diet under hospital observation; he was given as much as he would eat six times daily. Although nasal symptoms continued, he did not develop a recurrence of his previous fatigue, perspiration and weakness until the end of the third day. With the continuation of wheat in the menu his fatigue-perspiration syndrome persisted for a week and again began to subside on the second day of wheat elimination. With the avoidance of wheat he has remained symptom-free for the past year. At the end of six months of avoidance he had obtained a sufficient tolerance to permit the reinstitution of wheat in his diet. In recent months he has been eating an average serving on alternate or third days without the precipitation of any of his former symptoms.



## SUMMARY

The symptoms of weakness and fatigue unrelieved by a formerly adequate or excessive amount of rest are described as a result of chronic allergic reactions. Although occasionally associated with inhalant sensitivity, this clinical picture is more commonly the result of uncontrolled food sensitivity. It usually occurs in association with migraine, gastrointestinal or nasal allergy; it may exist without any other past or present evidence of clinical allergy. When it is the result of allergic reactions to food, the diet is not usually suspected and specific dietary offenders are rarely detected by the patient.

The fatigue syndrome of allergic origin is commonly associated with a negative physical examination, negative x-rays and other routine laboratory procedures. This manifestation of allergy must be carefully differentiated from other causes of fatigue and weakness, including the fatigue of both organic and functional origin. The mere absence of positive physical findings and laboratory reports does not justify the assumption that fatigue otherwise unexplained is the result of a psychosomatic disturbance.

Fatigue of undetermined origin, particularly if associated with other evidence of clinical allergy, should be studied by means of diagnostic procedures to detect specific food sensitivity. Perfunctorily performed skin tests with food allergens are not sufficient in view of the unreliability of such procedures. These cases must be studied by means of trial diets, either the standardized and detailed elimination diets as suggested by Rowe or diets based upon the results of feeding tests with several of the major allergenic foods.

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# INTRODUCTION OF ALLERGENS INTO THE SKIN BY INUNCTION WITH "INTRADERM"

## I. Additional Experimental Data on the Inunction Test

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THE penetration of "protein allergens" by inunction with a new type of vehicle into the grossly intact skin has been established in previous studies<sup>3</sup> on patients suffering from atopic dermatitis. This type of vehicle has now been trade-marked by the manufacturers<sup>†</sup> under the name, "Intra-derm." Further investigations have been carried out with the formula which was referred to as vehicle D in the previous publication, and which has proved to be the most satisfactory of the combinations tested: A mixed alkyl benzene sodium sulfonate, 2 weight parts, e.g., 20 grams; Antipyrine, 2 weight parts, e.g., 20 grams; Water, 2 volume parts, e.g., 20 c.c.; Propylene glycol, 5 volume parts, e.g., 50 c.c. Since the preceding publication<sup>3</sup> fourteen more individuals were tested. Moreover, the test series were repeated in a group of previously tested patients. The method of examination has been described in our foregoing report on this subject.<sup>3</sup>

As was the case in the previously reported series, no "false negatives" were seen in the more recently investigated individuals (44 allergens); i.e., there were no negative results in any case which reacted positively to scratch test with the same allergen. Altogether, comparative scratch and inunction tests comprise 770 series in sixty-seven individuals. Whereas our standard method has remained the comparison of the scratch test with inunction tests, some cases deserve mentioning in which there was a discrepancy in the results of intradermal injection and the scratch test. These cases of discrepancies between the two orthodox forms of skin testing are given in Table I, together with their responses to inunction tests.

It will be seen that in four cases (5 allergens) the inunction test was negative when a positive result was obtained with intradermal injection. On the other hand, with six allergens on four patients, inunction and intradermal tests were positive where scratch tests showed no reactions or only after repeated testing. One of these individuals showed a negative intradermal test with two other allergens, whereas inunction test as well as scratch test gave strongly positive results. In several other cases, pseudoreactions were seen after intradermal injection tests, which the inunction tests and inunction controls showed to be of the nature of an urticaria factitia. Although routinely applied control injections of saline had produced somewhat less whealing in these cases than the allergen injections,

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<sup>†</sup>Wallace Laboratories Inc. New Brunswick, N. J.

TABLE I. TABULATION OF DISCREPANCIES

Case	Sex	Age	Allergen	Inunction	Scratch	Intradermal Injection <sup>1</sup>
1. R.P.	M	11	horse dander	+	—(but in a few subsequent test series: +)	+
2. J.G.	M	17	horse dander	+	—	++
			dog hair	+	—	++
			dust	+	—	++
3. B.M.	M	12	coffee	+	—	+++
4. A.S.	F	25	egg white	++++	—(but in subsequent test series: +)	+
			silk	++++	++	—
			goose feathers	++	+	—
5. L.P.	F	3	silk	—	—	+
			goose feathers	—	—	w. + <sup>2</sup>
6. F.G.	F	20	horse dander	—	—	++
7. W.H.	M	67	pyrethrum	—	—(and patch test: —)	+
8. F.St.	F	3	milk <sup>3</sup>	—	—	+

1. The results of intradermal injection refer to the following concentrations:  
Dust—suspension of house dust 1:10 in saline.  
All epidermals, silk, pyrethrum—1,000 Noon units.  
All food allergens—0.05 mgm. except milk—0.01 mgm. and egg white—0.005 mgm.
2. w. + = weakly positive.
3. When child was kept on full diet (including milk) condition cleared up!

the character of an urticaria factitia was evident, after the injections were repeated in consequence of the revealing results of the inunction method.

Another point of interest regarding reactivity to inunction tests in general is the fact that not all (of the grossly intact) skin areas showed equal intensity of allergenic response. Whereas a positive reaction could be manifested by inunction in almost every skin area of our patients, there was a difference in degree inasmuch as whealing and erythema were more extensive on the back, and also in the apparently normal sites surrounding areas of active atopic dermatitis.

The stronger results on the back are in conformity with the preponderant reactivity of that skin area to scratch and injection tests as described by H. L. Alexander and F. S. McConnell<sup>1</sup>, H. L. Alexander<sup>2</sup>, L. W. Hill<sup>4</sup>, G. Piness and H. Miller<sup>7</sup>, and W. Schmidt.<sup>8</sup> The intensified response near the diseased sites corresponds with the similar observations in contact allergy, as, for instance, those of J. Jadassohn<sup>5</sup>, H. Stauffer<sup>9</sup>, M. B. Sulzberger and Ph. Kerr<sup>11</sup>, H. W. Straus and A. F. Coca.<sup>10</sup>

Besides, differences in intensity of the reactions were occasionally seen in symmetrically situated apparently normal sites in one and the same individual. For instance, a woman with allergy to silk, corn, and rye showed strongly positive reactions on the right lower leg, whereas the reactions were invariably very mild, or even absent, on the left lower leg. This difference was very obvious, not only in the inunction tests, but likewise in the scratch tests.

Special attention was given to the reaction of the palms to allergens. No positive reactions could be elicited there by inunction, in spite of many trials in suitable individuals who evidenced distinctly positive tests in other areas. Six infants were selected for these studies in order to exclude, as far as feasible, the possibility of the suppression of whealing in the palms by excess of horny material, as may be the case in adults. Nine allergens were inuncted at numerous occasions in these tender palms by means of Intraderm without producing any signs of a reaction, whereas the results were strongly positive in the other areas tested. The same experiment was carried out in two eleven-year-old boys, after their palms had been softened by a prolonged preparatory treatment with 10% salicylic acid-petrolatum and soaked in warm water and soap solution. The results obtained with five different allergens, each of which was applied several times, were the same as in the infants.

In order to ascertain the presence of sensitization in the palms, eighteen scratch tests were carried out on these areas in all these patients, including the infants. Necessarily, these tests were performed at different times than the inunction tests in the same areas. Ten different allergens were used and applied by scarification in the softest part, the center of the (left) palms. Controls with N/10 NaOH were carried out symmetrically in the other (right) palm.

Notwithstanding carefully marked scarification, notwithstanding the softness of the infantile skin, and notwithstanding the selection of palms with an intense reactivity of other skin areas to the same allergens, in general only weak reactions could be elicited in the palms. Strong whealing was seen only once, most of the other reactions were mild or doubtful appearances in the form of a diffuse, red elevation that was more persistent and somewhat larger than the traumatic effect in the control site. A further check was carried out by means of intracutaneous injections of the allergen in the palms. In response to these tests very distinct whealing appeared, the reaction being definitely stronger than in the corresponding control site of the other palm where saline was injected. However, the positive responses to intradermal injections were also considerably weaker than the reactions obtained by the same test in other skin areas of the same individual.

The absence of reactions in the palms after allergen inunction\* has been mentioned in a previous report<sup>6</sup> in connection with our histological findings. As the follicles furnish the main pathway for various substances entering the skin after application with Intraderm, the lack of follicles appears to offer a possible explanation for the failure of allergen inunction tests in the palms.

Meanwhile A. Walzer and S. S. Sack<sup>12</sup> reported that they did encounter absorption of cottonseed from grease bases through the palms, though

\*We wish to thank Dr. Gd. Rubin, New York Skin and Cancer Unit, for his suggestion to employ inunction tests in the palms.

at a very slow rate. This appears in some contradiction to our findings; but these authors used a "forceful manner"<sup>13</sup> of application.

As was expected, our results of scratch and intradermal injection tests do give evidence of the presence of sensitization in that site. However, the comparatively weak response to these applications leads to the assumption that here, too, the distinct anatomical and functional differences between palms and other skin areas must be responsible for the observed difference of reaction.<sup>‡</sup>

Nevertheless, the reduced whealing in the palms after intradermal injection indicates that a hindrance of passage through follicles cannot be the only reason for the weak reactivity of this area. The tension of tissue structures may somewhat impair a circumscribed accumulation of edematous liquid and thus contribute not only to the weaker response after allergen injection, but also to the insufficient outcome of the two other methods of testing, especially of the scratch tests. Further studies of this question are in progress.

#### SUMMARY

1. Seven hundred and seventy comparative test series of allergen application by inunction with "Intraderm" and by scarification in sixty-seven individuals with atopic dermatitis showed complete agreement of positive reactions by either method. If the outcome of intracutaneous tests is taken as base line, false negatives were occasionally obtained with the inunction method. However, the scratch tests failed to show positive reactions twice as frequently.

2. Differences in reactivity were seen sometimes in different skin areas of the same patients to the same allergens applied by inunction as well as by scarification. Stronger reactions were encountered in the surroundings of a diseased area than in farther distant sites. Besides, in a few individuals, differences in intensity of the reactions were observed regularly in symmetrical, grossly normal skin regions.

3. The skin of the palms invariably failed to respond to allergen application by inunction, in spite of strongly positive reactions obtained in the other skin areas of the same individuals, and in spite of the softness of the palmar skin in infants who were used for these tests. Similarly, the scratch tests gave only very weak reactions in the volae manus. The presence of sensitization in this site came more distinctly to the fore with intradermal allergen injection, though the response was weaker than in other parts of the skin. These results are explainable by anatomical peculiarities of the skin in the palms.

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<sup>‡</sup>Regarding the scratch tests, the assumption that the presence of follicles is important for the production of all wheal reactions is supported not only by our results in the palms of children, but also by the fact that several tiny follicular wheals along the edges are rather frequently observed in positive reactions to scratch test applied in one of the usual locations. It is conceivable that the soaked follicles might provide an efficient drainage towards the deeper structures in the cutis, in addition to the fine cleft at the base of a scratch.

# PASSIVE TRANSFER OF EXPERIMENTAL CONTACT DERMATITIS WITH THE URBACH-KOENIGSTEIN TECHNIQUE

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**D**ERMATITIS acquired by contact is universally regarded as the result of a strictly local cutaneous hypersensitiveness; consequently, it is generally agreed that (1) the only organ affected by the sensitization is the skin; (2) the sensitiveness is caused by repeated contact with the skin itself; (3) the sensitiveness can spread only by contiguity; (4) in conformity with the preceding statements, the sensitiveness cannot be transmitted by means of blood serum, since the former is confined to the cells of the sensitized zones and does not involve the tissue fluids. This last point is of considerable importance, as it supposedly marks the fundamental difference between contact dermatitis and atopic dermatitis. The above views seem to be corroborated by certain experimental findings, namely (1) that cutaneous hypersensitiveness can be transmitted through skin grafts (Bloch<sup>2</sup>, Naegeli et al<sup>6</sup>, Urbach and Sidaravicius<sup>10</sup>; (2) that the extension of the hypersensitiveness can be limited by means of cutaneous incisions reaching down to the muscular aponeurosis (Strauss and Coca<sup>8</sup>); (3) that it is apparently impossible to transmit contact sensitiveness through the serum (Sulzberger<sup>9</sup>, W. Jadassohn<sup>3</sup>).

However, reports in the literature are not unanimous in supporting these conclusions. Some authorities point out that the transmission of sensitiveness by graft does not exclude the possibility of humoral transmission. Moreover, limitation of sensitiveness through an incision could not be confirmed by Landsteiner,<sup>4</sup> Anke<sup>1</sup> and Schnitzer.<sup>7</sup>

On the other hand, notwithstanding the failures of Sulzberger<sup>9</sup> and others to achieve passive transfer, Urbach<sup>12</sup> has succeeded in transmitting epidermal hypersensitiveness to primula and to turpentine through the vesicatory fluid. Subsequently, this author<sup>11</sup> was able to achieve passive transfer of hypersensitiveness with vesicatory fluid to arsenic, arnica, nickel and flour. Using the technique of Urbach and Koenigstein<sup>10</sup>, other authors (Perutz, Fuhs and Reihl, Musger, Schreiner, Scerbakov, Ensbrenner, van Dishoeck and Roux, Biberstein, Konrad, Santalov, Zitzke, Hajos and Mohrmann, Brandt and Konrad, Flarer, Melczer and Wlassicz, Fellner, Engel and Vigliani<sup>10</sup>) have achieved the transmission of contact dermatitis caused by arsphenamine, primrose, turpentine, ammonium persulfate, atropine, orthoform, novacain, asparagus and other substances.

## ORIGINAL EXPERIMENTS

In a previous report, one of us (Mom<sup>5</sup>) described a phenomenon which can be explained only on the basis of a humoral mechanism, as far

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## CONTACT DERMATITIS—BALLESTERO AND MOM

TABLE I. SUMMARY OF PASSIVE TRANSFER OF EPIDERMAL HYPERSENSITIVENESS IN CONTACT DERMATITIS

Donor			Recipient						
Case No.	Day after eliciting contact on the donor	Concentration 2-4 dinitrochlorbenzene	Time in Hours after the Passive Transfer						
			Cantharides fluid			Donor serum			Controls
			Fixation time	Reaction time	Intensity of response	Fixation time	Reaction time	Intensity of response	
1	21	1:50 (1)	24	96	e3-p2-pr2	48	48	e1	e1
			48	48	e2-v1-pr1	—	—	—	e1
			96	48	e2-v1-pr1	—	—	—	e1
2	21	1:50 (1)	24	48	e1	48	48	e1	e1
			48	48	e2 pr2	—	—	—	e1
			96	24	e2-v2-pr3	—	—	—	e1
3	21	1:100	24	48	e2-p2-pr1	48	48	e1	e1
			48	24	e3-v2-pr2	—	—	—	e1
			96	24	e3-v3-pr2	—	—	—	e1
			168	12	e3-v3-pr3	—	—	—	e3
4	42	1:100	24	96	e2 pr1	48	96	e1	e1
			48	24	e3-p1-pr1	—	—	—	—
			168	24	e3-v1-pr3	—	—	—	e3
5	7	1:50 (1)	24	24	e2-p2-pr2	48	—	—	e1
			96	24	e3-v2-pr2	96	48	e1	e1
			168	24	e3-v3-pr3	—	—	—	e1
6	7	1:100	96	24	e2-p2-pr3	—	—	—	e2
7	7	1:1000	96	24	e2-v1-pr2	—	—	—	e1
8	7	1:1000	120	24	e3-v1-pr2	—	—	—	e2
9	7	(2)	24	—	—	48	—	—	e1
			96	—	—	—	—	—	—

(1) Concentration was double that used on the donor.

(2) The provoking agent was a solution of paraphenylenediamine.

The transmitting medium was vesicular fluid produced by cantharides paste. With the exception of Cases 6, 7 and 8, there was an equal transference with blood serum.

NOTATIONS: e—erythema; p—papules; v—vesicles; pr—pruritus. The number which follows the letter indicating the type of lesion is a conventional indication as to the intensity of the response (See Rev. Arg. Dermatosisif., 26:419, 1942). 1—slight; 2—fairly strong; 3—great intensity.

as the spread of dermatitis is concerned. If four cutaneous zones of the abdomen (two on each side of the midline) are sensitized with 2-4 dinitrochlorbenzene, and one of these zones is exposed to a second contact with the chemical, a typical eczematous reaction makes its appearance in all four zones, including those which were not stimulated a second time. This phenomenon occurs in any sensitive zone, and is followed by a flare-up of any pre-existing spontaneous eczema. We believe that the repeated failures to transfer sensitiveness by the Prausnitz-Kuestner method can be explained by the insufficient concentration of the transmitting substances in the blood serum. That is the reason why we, in our experiments, employ the technique with vesicatory fluid of Urbach.<sup>13</sup>

## METHOD

*Donor.*—The donor is sensitized in the manner we described in detail in a previous article (Mom<sup>5</sup>). Seven days later, the second contact is applied,

following the same technique. Once the reaction has passed and an additional period of time has been allowed to elapse (Table I), a blistering Cantharides plaster is applied. We used the following formula (Euphorbia 14 gm., turpentine 20 gm., wax 33 gm., cantharides 33 gm.). This paste is applied with a piece of filter paper on an area of approximately 1

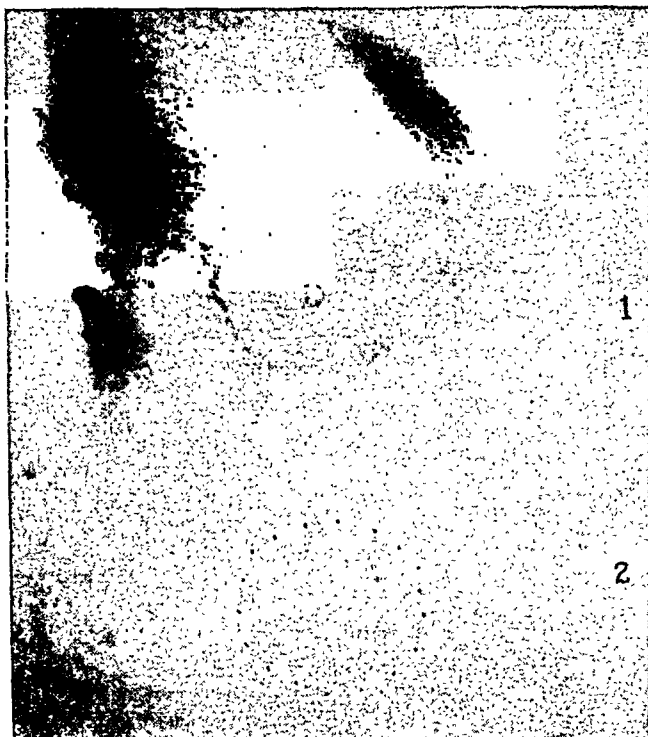


Fig. 1. Passive transfer by Urbach-Koenigstein technique.

*Recipient.*—First injection in 1 of 0.05 c.c. of centrifuged blister exudate; second application in 1 and 2, forty-eight hours thereafter of 0.03 solution of dinitrochlorbenzene 1/1000.

After twenty-four hours, the transfer area (1) showed up a well-marked vesicular dermatitis, while in the site of the control (2) only a very slight erythema appeared.

*Donor.*—Twenty-eight days prior to the transfer, the donor was sensitized by contact with dinitrochlorbenzene. Dinitrochlorbenzene was applied again (eliciting contact) twenty-eight days before the transfer, inducing a dermatitis which cleared up in eight days. Twenty-four hours before the transfer, the vesicatory was applied to the zone where the dermatitis had been induced; the resulting exudate was used for the transfer.

sq. cm. It is then covered with cellophane and waterproof adhesive tape. The fluid makes its first appearance about twelve hours later, and reaches its maximum in twenty-two hours.

*Recipient.*—The liquid is withdrawn from the vesicle through a needle connected to a tuberculin syringe and then immediately injected intradermally into the recipient at the rate of 0.5 c.c. per papula. If this amount is found to be sufficient, the injection is repeated in several sites on the abdomen along the mammary line. In most of the experiments performed the donor's blood serum was injected into symmetrical areas. After periods of time varying between twenty-four and 168 hours, 0.03



c.c. of solution of dinitrochlorbenzene in acetone in the concentration (1:1000) previously used for the second contact in the donor, is applied to every infiltrated zone. We should like to mention at this point that the concentrations and eliciting doses employed by us in accordance with our technique are so weak that they rarely sensitize normal healthy individuals. One application of dinitrochlorbenzene is made at a point on the skin which has not previously been treated and this site is used as a control. The intensity of reaction is expressed in the manner described in the footnote of Table I.

#### RESULTS

We have invariably obtained positive results which we have listed in the accompanying table. We should like to stress that the transmitted reactions reproduce contact dermatitis that is typical both in appearance and evolution. We can also state that between the seventh and forty-second days the skin in which an experimental contact dermatitis has been produced may yield an exudate through the action of the cantharides plaster which transmit sensitiveness to dinitrochlorbenzene to a recipient. This sensitiveness is revealed by the application of dinitrochlorbenzene in concentrations equivalent to those used for the second contact in directly sensitized individuals. The transmitted reactions are similar in appearance and course to the manifestations of typical contact dermatitis. This reaction varies in accordance with the fixation time—that is, the length of time between the injection of the fluid and the application of dinitrochlorbenzene. The longer the fixation time, the sooner the erythema makes its appearance following the second contact and the more intense the reaction. In one experiment, there were no reactions when the second contact was made with paraphenyldiamine, thus proving that the phenomenon is highly specific.

#### DISCUSSION

Studying the passive transfer of contact dermatitis, the question arises as to whether the transferring substance is merely some eczematogenous agent, capable of inducing dermatitis, or whether it is on the contrary something similar to a reagin. Obviously, the re-activation of eczema during the course of experimental dermatitis or by means of injection of vesicle fluid into cutaneous zones, affected with spontaneous eczema, indicates that the fluid possesses eczematogenous properties. In that event the sensitized zones would, in effect, be areas of subclinical eczema which could be activated by these substances. Moreover, in addition to these general eczematogenous properties, the transmitting fluid possesses other more specific properties, since it sensitized the recipient's skin to dinitrochlorbenzene but evoked no response when such a powerful excitant as paraphenyldiamine was used. We can scarcely attribute this to an eventual sensitization through the traces of dinitrochlorbenzene left

on the skin of the donor. It is unlikely that, as late as twenty-one or forty-two days after the application of 0.03 c.c. of a 1:1000 solution, there should remain a sufficient quantity of the substance to produce a primary sensitiveness when diluted in the exudate. Nor can the phenomenon which occurred twenty-four hours after the injection be attributed to a primary hypersensitiveness, for such a condition generally takes about six days to develop. It has yet to be proved that the substances we find in the vesicles are identical with reagents. However, while we cannot as yet evaluate the substances in the vesicular fluid accurately, there can be no doubt that they are of the utmost importance in the origin and spread of experimental contact-type dermatitis and of spontaneous eczema.

## SUMMARY

The successful passive transfer of experimental contact dermatitis induced by dinitrochlorbenzene is described. It can be achieved only with vesicatory fluid according to the Urbach-Koenigstein method and not with blood serum used in the Praussitz-Kuestner method. It is believed that the substances present in the vesicatory fluid are identical with antibodies and that they are responsible for the origin and spread of experimental contact dermatitis and probably also of spontaneous eczema.

In addition the transmitting fluid has exciting properties which become apparent on any already existing eczema.

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*Migraine Headaches Relieved by Hypoglycemic Reaction; Report of Two Cases.*  
Tillim, S. J.: *Ann. Int. Med.*, 20:597, 1944.

The author reports two cases in which a diagnosis of migraine had been made, and for which previous therapy had resulted in opiate addiction. Because "induced hypoglycemia is antispasmodic and antagonistic to sympathetic activity," such a procedure was employed in relieving these headaches. The dosage of insulin required varied from time to time, with the gauge being clinical manifestations of hunger, thirst, diaphoresis and somnolence. Coma was not required. The intravenous route was productive of more rapid effects. Two cases are reported in which such hypoglycemic measures gave prompt and prolonged (four months) relief from subsequent attacks, all of which were aborted by the use of insulin reactions.

## PARENTERAL USE OF DIHYDROERGOTAMINE IN MIGRAINE

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THE incapacitating and recurrent nature of migraine is such that the allergist, endocrinologist and neurologist are under constant pressure to find means of prevention. Once the attack is under way, however, symptomatic measures must be employed. Until the advent of ergotamine tartrate (gynergen), therapy was limited by the relative ineffectuality of the salicylates and coal tar derivatives on the one hand and on the other by the habituation danger attendant to the use of the opiates. Ten years of experience with ergotamine tartrate has shown its effectiveness in aborting or relieving attacks of migraine; reports of its efficacy range from 70 to 98 per cent.

Because the grateful relief afforded to the cephalgia by it has had the accompaniment of nausea, uterine stimulation, and powerful, persistent peripheral vasoconstriction in a significant proportion of cases, an equally efficacious agent without these drawbacks would be desirable. The closely related dihydroergotamine (D.H.E.-45 Sandoz) has been investigated pharmacologically; it produces a paralysis of the sympathetic nervous system similar to ergotamine tartrate, but is only one-tenth as toxic. It has no uterine effect *in vivo* or *in vitro* and is a less powerful vasoconstrictor than ergotamine tartrate, experimental gangrene having been produced only with great difficulty.

### SELECTION OF CASES AND METHOD

The twenty cases selected for trial were classical cases of migraine in whom the clinical response to ergotamine tartrate was already known. Seventeen out of them had obtained relief from ergotamine tartrate and three had not. Fifteen were females and five males; the age range was from fifteen to fifty-eight, the average being thirty-four. Four of the group had blood pressures below 100 systolic and three above 150 systolic; the remaining 13 had systolic blood pressures in 110 to 130 range. Without exception the cases conformed to the following diagnostic criteria; (1) positive family history of migraine, asthma or seasonal hay fever (other allergic manifestations were subject to too much error); (2) a definite aura; (3) paroxysmal periodic headaches always one-sided in the beginning of the attack, although in some cases involving both sides as the attack went on; (4) an ocular manifestation such as photophobia, scintillating scotomata or blurred vision; (5) nausea, with or without actual vomiting.

All cases were observed for changes in pulse rate, blood pressure, changes in amplitude of radial, dorsal pedis and posterior tibial pulsations and changes in color and temperature of the extremities. Since nausea was already an integral part of the migraine syndrome, it was considered as

due to the drug only if the nausea increased within one hour after the injection or did not decrease after the headache had subsided. The standard dosage was 1 mg. (1 c.c. ampoule) intramuscularly.

#### RESULTS OF DIHYDROERGOTAMINE TREATMENT

Complete or very marked relief of the headache and associated symptoms were obtained within eighty minutes in seventeen (85 per cent) of the twenty cases. The three cases obtaining no relief were those in which ergotamine tartrate had been ineffective also.

The following individual cases are of interest:

1. A woman seven weeks pregnant, relieved of her headache without any cramping or spotting.

2. Three cases of migraine associated with menstruation, all relieved. No cramps or change in menstrual flow was observed in these, but in two of them ergotamine tartrate used in previous attacks had caused uterine cramps and irregularity.

3. A woman in whom inter-menstrual cramping had always been evoked by ergotamine tartrate but whose headache was relieved by dihydroergotamine without incident.

4. A man (an inveterate heavy smoker) with whom the relief of headache by ergotamine tartrate had caused blanching and pain in his toes. Dihydroergotamine relieved his symptoms without any change in color or sensation of his toes.

No significant changes in blood pressure, pulse rate, peripheral arterial pulsations, skin color or skin temperature were observed in this group. Of the seventeen cases in which headache had been relieved, only one patient suffered nausea ascribable to the dihydroergotamine; eight of this group had previously suffered nausea due to ergotamine tartrate. In the group of failures the characteristic nausea of the attack was neither augmented nor diminished by the dihydroergotamine; one of these had previously been nauseated by ergotamine tartrate.

#### COMMENT

It would appear that Dihydroergotamine is equally as effective as Ergotamine Tartrate for the relief of typical migraine but has the following advantages over the latter: (1) lack of uterine stimulation, (2) greatly lessened incidence of nausea, (c) absence of demonstrable effects on vessels of extremities on intramuscular injection, (d) absence of changes in blood pressure or cardiac rate on intramuscular injection.

#### SUMMARY

1. Of twenty classical cases of migraine the same seventeen cases (eighty-five per cent) relieved by ergotamine tartrate were relieved by dihydroergotamine.

2. Dihydroergotamine did not cause uterine cramps in any of the

fifteen female patients, one of whom was pregnant and three of whom were menstruating.

3. Only one (five per cent) of the twenty cases suffered nausea ascribable to the dihydroergotamine. Nine (forty-five per cent) had nausea ascribable to ergotamine tartrate.

4. Dihydroergotamine used intramuscularly produced no demonstrable effects on (a) pulse rate, (b) blood pressure, (c) pulsations of radial, dorsalis, pedis, and posterior tibial arteries, and (d) temperature and color of the extremities.

450 Sutter Street, San Francisco, California

Thanks is given to Mr. H. Althouse of the Sandoz Chemical Company for supplying the dihydroergotamine used.

## Introduction of Allergens into the Skin by Inunction with "Intraderm"

(Continued from Page 434)

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# SUCCESSFUL THERAPY OF A DERMATOLOGIC SYNDROME WITH L. CASEI FACTOR (FOLIC ACID)

## Preliminary Report

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IN an extended experience in the diagnosis and treatment (by avoidance) of the numerous symptoms and other consequences of the newly defined familial nonreaginic food allergy, a growing number of cases have been encountered who, after all of the food allergens have been identified and avoided, complain of more or less severe symptoms that were apparently not allergic.

Empirical experimentation in the first few cases revealed that the symptoms are in all instances immediately caused by a deficiency of members of the group of water-soluble vitamins known as B-Complex, and that those members are not any of the previously identified and synthetically produced thiamin, niacin, riboflavin, pyridoxine and pantothenic acid.

Later, two kinds of these symptoms had to be distinguished; one kind is essentially nervous, while the other is cutaneous, appearing as an intractable dermatitis. Moreover, it has become clear that these two abnormal manifestations are caused by a deficiency of two different substances.

The first three patients exhibited only the nervous symptoms—*anorexia*, weakness, uncontrollable nervousness and insomnia. The fourth patient suffered the nervous symptoms in marked degree and also a long-standing scaly, inflammatory eruption of both legs.

Three other patients showed no nervous symptoms but a widespread weeping eruption of limbs, body and face.

The nervous symptoms of one of the first three patients have been completely controlled for several years with large oral doses of a liver concentrate containing practically none of the L. casei factor ( $0.11\text{ }\mu\text{g}$  per c.c.).

The nervous symptoms of the third and fourth patients and the dermatitis of the fourth patient are controlled by large doses of yeast (baker's or brewer's). Deprivation of the yeast in these two cases causes prompt recurrence of the nervous symptoms and recurrence of the dermatitis in the fourth case after two weeks, notwithstanding ample dosage, during that time, of all of the "synthetic" members of the B complex mentioned above.

The fifth and sixth patients (D. J. and R. L.), long sufferers from weeping dermatitis, were practically well after a few weeks of oral treatment with large doses (16 to 18 capsules daily) of vitamin B complex\* (Fall, 1944). In January, 1945, the capsules of vitamin B complex were discontinued entirely and the two patients took three capsules daily of a dried crude concentrate of L. casei factor ("folic acid") prepared from liver. Each capsule contained approximately 400 micrograms of folic acid

\*Lederle Laboratories, Pearl River, N. Y. Each capsule contains from 10-20  $\mu\text{g}$  of L. casei factor ("folic acid").

which was approximately the estimated content of 20 capsules of the vitamin B complex.

About four weeks after this change was made the dermatitis began to recur, and shortly afterward the dose was increased to four or six capsules of the concentrate of the *L. casei* factor. About two weeks after this increase the dermatitis was healed and remained so during the succeeding six weeks or longer.

The seventh patient, a nurse who, for many years, had suffered a widespread weeping dermatitis affecting the limbs, face and scalp, has been under the care of Dr. Louise E. Tavs in Chicago. Dr. Tavs reports marked improvement following treatment with the concentrate of the *L. casei* factor.

On August 11, 1945, R. L. (Case 6) who had been slightly underdosed (lesions recurring), began to take 3 mg. daily of synthetic folic acid\* (Lederle), and on August 14, D. J. (Case 5) began to take 2.5 mg. of the synthetic substance, both patients discontinuing the liver concentrate. On August 21, R. L. was so greatly improved that the dose of folic acid was reduced to 2.5 mg. with the idea of determining the minimal maintenance dose.

On August 26 it was learned that lesions had begun to recur in D. J. (Case 5) on August 21, and had become progressively worse. The dose was then increased to 3.5 mg. and on the following day R. L. (Case 6) was advised to return to the daily 3.0 mg. although his skin was still clear (excepting a few "spots" on the hands).

On September 21 both patients were "better than ever," D. J. (Case 5) having "two red scaly spots on one ankle."

This experimental study represents practically a continuation of that reported by Paul Gross† in 1941, although I did not learn of that report until I was preparing to write the present one. I quote the following passages from Gross' paper.

"This paper deals with cutaneous eruptions not quite conforming with any well-known dermatologic entity. The main feature common to all these conditions was their response to parenteral liver therapy, which suggested that they were due to a deficiency of the Vitamin B-Complex.

"Further studies and a more rational therapy with *synthetic products* are necessary to clarify the role of vitamin therapy in this disease."

Gross assumes an "underlying disorder of digestion and assimilation," an assumption that falls in with my own thought that that disorder may be allergic. All of my four patients were food allergic. If all patients in, say, 100 consecutive cases are found to be food allergic, this would answer the question.

The further exploration of this interesting problem evidently must be

\*Synthesis reported in Science, 102, Aug. 31, 1945, from Lederle Laboratories and Calco Chemical Company.

†Nonpellagrous Eruptions due to Deficiency of Vitamin B-Complex. Arch. Dermat. & Syphilol. Mar. 1941, 43:504-531.

undertaken by dermatologists who are conversant with the possible allergic implications.

Dr. Paul Gross was good enough to read the foregoing and to point out some mistakes in the dermatologic aspect of the descriptions, which have been corrected. He also wrote a discussion of the paper which he permits me to append.

#### DISCUSSION

PAUL GROSS, M.D.—I am quite optimistic on the basis of Dr. Coca's report, that folic acid may be a valuable therapeutic agent in certain conditions, which we have found to respond to parenteral liver therapy.

It has been my experience that only sufficient quantities of a crude liver extract could be expected to have an effect on certain skin eruptions, and even then, the large doses of crude liver which we used in former years seem at times to stop short of a complete curative effect. When synthetic vitamins of the B complex became available I tried to duplicate these results with them, beginning with nicotinic acid, later riboflavin, pyridoxine, pantothenic acid and a combination of all the "knowns," in a high potency. The results were disappointing except in sporadic cases. Most disappointing was pantothenic acid, because as the most important member of the "filtrate fraction" of the B complex in animal experiments it had held out hopes of being useful in clinical experiment in humans. Neither did the addition of biotin to a parenteral B complex duplicate the results of the crude liver preparations.

The situation became further complicated when the crude liver extract used in our original work was changed in its composition, which resulted in a dilution of the important crude filtrate fraction in favor of a higher unitage of the A. P. factor. If you realize that we used to give as much as 10 c.c. of the crude extract, but could not administer more than 5 c.c. of the diluted liver intramuscularly, you will understand that the therapeutic effect previously obtained could not be reproduced. Preparations containing synthetic B vitamins with liver extract are a welcome addition to our oral and parenteral vitamin therapy, but the amount of the natural crude B complex is too small to supply enough of the unknown factors.

I have found the oral administration of soy bean lecithin the most suitable way of adding choline and inositol to B complex therapy, especially when high serum cholesterol findings indicate a disturbance of liver function and fat metabolism. It is interesting that the treatment of liver cirrhosis by nutritional factors present implications similar to those encountered in the treatment of skin eruptions, related to a conditioned deficiency in the vitamin B complex. The inadequacy of the B complex and synthetic vitamins and the severe liver damage resulting from a profound nutritional failure have been recently demonstrated in pellagra of children.†

In my paper on nonpellagrous vitamin deficiencies of the B complex I raised the question, whether the effect of the parenteral liver extract is due to the route of administration or to the presence of other factors than those which have become available in synthetic form and can be administered in therapeutic amounts. The synthesis of folic acid thus makes another vitamin of the B-complex available which can be tested as to its efficacy when given per os in sufficient quantity. The relationship of this substance to bacterial synthesis in the intestinal tract of the rat, its interaction with other B-complex factors and the symptomatology of the folic acid deficiency of experimental animals makes the clinical investigation of this vitamin very interesting.

What are the skin conditions in which a therapeutic effect of parenteral liver therapy can be demonstrated? This therapy has been widely accepted by derma-

†Gillman, Th. and Gillman: Infantile pellagra. J.A.M.A., 129:12, (Sept. 1) 1945.



tologists following my publication, in cases of widespread eruptions, classified by the misleading name of seborrheic dermatitis, and in generalized exfoliative erythroderma originating from seborrheic dermatitis, but at times precipitated by extraneous factors, especially arsphenamines, bismuth, arsenic, gold and other hepatotoxic drugs, like sulfonamides. This type of exfoliative erythroderma should be differentiated from generalized skin eruptions of an eczematous type, which are based primarily on an allergic reaction to drugs, especially arsphenamines.

The factors predisposing to a conditioned deficiency are apparently rooted in the constitutional disturbance summarized as the "status seborrhoicus." Gastric hyp acidity on an acidity, disturbances of carbohydrate and fat metabolism, hyposthenia, and menstrual dysfunction are some of the features which can be frequently observed in such patients. Some cases resembling seborrheic dermatitis showed such dramatic response to liver therapy that from this fact and from the dietary history of these patients a primary nutritional failure could be assumed. I believe that there is a definite clinical pattern in those skin eruptions which are the result of a disturbance of cellular metabolism due to deficiencies, and which finds its simplest expression in typical pellagra. The character of the skin lesions, the distribution, the production of isomorphous reactions by mechanical, physical and chemical trauma distinguishes these conditions from the explosive skin reactions due to epidermal and dermal allergy. Susceptibility to pyogenic infections in seborrheics is a well-known fact and has its analogue in the pellagrous glossitis and Vincent's infection and the presence of hemolytic organisms in the perleche of the typical ariboflavinosis.

Another disease which follows a similar pattern is pityriasis rubra pilaris. I have described several cases of this disease which completely responded to parenteral liver therapy. There is also a vitamin A deficiency present in this disease as shown by Brunsting and others, but the therapeutic result with vitamin A therapy is not always complete. The clinical features again suggest a combined deficiency, since the follicular keratosis is not the sole pathology. Psoriasiform lesions and erythroderma, partial or generalized, palmar and plantar keratoderma and in some instances typical photosensitivity, combined with isomorphous reaction to mechanical irritation, point to a pellagra-like deficiency in the vitamin B complex. The interrelationship between vitamin A and B complex deficiency seems to have a real basis in the complicated mechanism of absorption and utilization of vitamin A. The combination of therapeutic doses of vitamin A with yeast or other crude sources of the B complex may obviate the necessity of using vitamin A concentrates in doses of several hundred thousand units per day.

The usefulness of the vitamin B complex in dermatology is by no means confined to the conditions described. It will be interesting to try folic acid therapy in a variety of well-defined dermatologic entities in which a therapeutic response to B complex therapy has been observed. This should include cases of chronic allergic eczema, which at times is favorably influenced by parenteral liver therapy.

The question whether substances like vitamins and amino acids can reduce the allergic reactivity, rooted in the cells of the shock organ or in the autonomic nervous system, should be further investigated by animal experimentation as well as in clinical studies. There is sufficient empirical evidence to encourage this work. It would also seem justified to re-open the problem of arsphenamine sensitization in guinea pigs. The deduction that ascorbic acid was responsible for the action of green fodder, was made before the postulation of a "grass juice factor" and its recent identification with folic acid.

# SINO-BRONCHIAL SYNDROME COMPLICATING ATOPIC ASTHMA IN CHILDREN

## Treatment by Roentgen Ray

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**B**EFORE discussion of the subject indicated by the title of this article, it may be well to preface our remarks with the general concept which we have of the asthmatic individual and the management of the asthmatic state.

We believe that the asthmatic is an individual of particular susceptibilities manifesting a fundamental constitutional defect which as yet we have no way of altering. We do believe also that this constitutional defect will manifest itself in various ways from time to time throughout the life of the individual, sometimes mildly, sometimes explosively, and that the manifestation may be one of a variety of clinical symptoms. Also, we believe that the factors which precipitate these constitutional manifestations may vary widely from time to time during the lifetime of the individual and that any evaluation of these factors must be considered only for the moment at which the observations concerning them are made. Not only may these factors vary, but the resulting symptoms produced by each individual factor may vary from age to age. These factors may be allergic sensitivity, infection, physiological defects, intercurrent diseases, etc. Thus a child may have successively eczema, rhinitis, and asthma, all resulting from the same or closely related factors at successive age periods. Or he may have asthma resulting successively from several types of allergens, infection or even psychosis. This process continues throughout the individual's life. If this fundamental concept approaches the true state of affairs it becomes apparent that our efforts and therapy against asthma resolves itself into a succession of procedures, each determined by the indications of the moment. Figuratively speaking, we may consider ourselves as assistants in minimizing the effect of lengthening the interval between, or preventing the development of a succession of episodes whose importance will vary but, if not controlled, in their summation will finally result in the asthmatic invalid.

The usual investigation attempting to identify allergic factors and the management following such an investigation, occasionally fails to diagnose all factors or to control all symptoms in some asthmatic children. This may be due to many factors not in the province of this presentation to discuss. Frequently symptoms will occur in children who are under apparently adequate allergic management and for which no atopic etiology is demonstrable. In some of these we think the sino-bronchial syndrome may be identified as at least one factor in the production of otherwise

# SINO-BRONCHIAL SYNDROME—DUTTON AND FUCHLOW

## DIFFERENTIAL DIAGNOSIS

	<i>Asthma Due to Atopy</i>	<i>Asthma Due to Sino-bronchial Syndrome</i>
1. Onset	Eczema, hay fever, asthma triad	Asthma begins with colds
2. Duration of Attacks	Paroxysmal, short duration	Gradually developing, longer duration
3. Fever	Not usual	Usual
4. Response to Adrenalin	Good	Poor
5. Leukocytosis	Infrequent	Frequent—Moderate to high
6. Sedimentation	Very slow	Normal or rapid
7. Nasal Smears	Eosinophilic	Neutrophilic
8. Bacteriology	Indifferent	Usually streptococcal pneumonia or staphylococcal
9. X-Ray Chest	Minimal changes	Striking changes
10. X-Ray Sinus	Minimal changes	Striking changes
11. Seasonal Incidence	Not seasonal or corresponds to pollen season	Winter or change of weather

unexplained symptoms. The sino-bronchial syndrome may be defined as that involvement of the sinus membrane by an infectious process of sufficient intensity to have implanted itself secondarily upon the bronchial mucous membrane by virtue of postnasal drainage. Admittedly, there may be considerable difficulty in differentiating the sinus involvement due to such a chronic infection from that due to allergy. The diagnosis of this syndrome requires careful observation and study. It can only rarely be made hurriedly.

The symptoms of the sino-bronchial syndrome as they occur in the allergic asthmatic child are generally rhinitis, postnasal drainage, cough, wheezing, and fever. The duration of these attacks is generally four days to two weeks and the patient appears quite ill. The onset is generally slow in contrast to the rapid onset of the atopic asthma attack and the duration is generally considerably longer.

The physical findings are not strikingly different from those found in atopic asthma. In the sino-bronchial syndrome the attacks of asthma are more likely to have moisture demonstrable in the lung fields, the pulse is generally more rapid, and the breath sounds resemble those of bronchitis more than the typical expiratory wheezing as with the asthmatic. It is not unusual to see attacks of this nature interspersed with attacks of typical atopic asthma in the same patient. The table summarizes the point of differential diagnosis and laboratory data.

In the diagnosis of this syndrome, the nasal smears are of the utmost importance. Neutrophilic leukocytes, generally with many streptococci, pneumococci, or staphylococci, and with only a few or no eosinophiles present are a constant finding in upper respiratory infections. This is in sharp contrast with the eosinophilic predominance in uncomplicated atopic asthma.

The technique of obtaining the smears is quite important, as not infrequently an improperly selected sample will fail to be conclusive in the

findings. We find these smears of most usefulness to us when done serially, following the patients from attack to attack and through episodes of different characters. By them it is not infrequently possible to identify allergic episodes with certainty followed by infectious episodes which fail to respond to the allergic management.

The blood count usually shows some indication of an infection either by elevation of the white count, elevation of the polynuclear percentage, or elevation of the immaturity index.

The sedimentation rate may also reveal an infection. It is almost always either normal or rapid in contrast to the usual delayed sedimentation rate in the uncomplicated atopic episode.

The child with the sino-bronchial syndrome will usually have higher temperature and of longer duration than the fever which sometimes accompanies simple atopic asthma in children. Admittedly, fever may accompany typical atopic asthma, but in our opinion it is a more striking feature of the attacks due to the sino-bronchial syndrome.

The response to palliative therapy generally offers some information concerning the diagnosis of these conditions. In atopic asthma adrenalin and ephedrine usually give prompt and efficient control of symptoms. This is generally not the case in those asthmatic attacks accompanying the sino-bronchial picture.

As a rule, some aid in arriving at the diagnosis may be gained by studying the periodicity of the attacks. In general, atopic attacks are more inclined to be periodic, particularly those associated with pollenosis, while the sino-bronchial syndrome produces symptoms either at irregular intervals or at intervals associated with changes of the weather or during periods of inclement weather.

The x-ray appearance of the chest in the atopic asthmatic generally shows minimal changes, while in the sino-bronchial syndrome the changes are frequently striking, being chiefly accentuation of the bronchial markings with coalescence of the hilar shadow and at times a diffuse reaction suggesting pneumonitis.

X-ray of the sinuses generally in the allergic state show minimal changes while those in the sino-bronchial syndrome often show striking changes characterized by hyper-plastic membrane. It should be noted that an evaluation of the sinus pathology is best made in intervals between acute attacks. By so doing we avoid those confusing changes in the sinuses that accompany acute colds or other upper respiratory infections and which may not be a permanent feature of the case at all.

It must be emphasized that in differentiating asthma due to the sino-bronchial syndrome from that due to atopy, all of these considerations must be given their proper evaluation. No single feature mentioned carries sufficient weight to make the diagnosis and generally the evaluation of the sino-bronchial syndrome can only be made after a period of observation covering a number of months and after adequate allergic manage-

ment has been carried out for a sufficient length of time to permit evaluating its effectiveness in controlling symptoms.

We have made many attempts to control the sino-bronchial symptomatology by various means: chemo-therapeutic, vaccine, and otherwise. We have found that one of the most effective instruments at our command to control this picture is Roentgen treatment.

The indication for this treatment is a well-established diagnosis. The treatment is best carried out in the chronic phase and the technique used varies. Generally about 400 roentgens over the sinuses and 800 to 1400 roentgens to the chest in four to six daily treatments are given. Not infrequently during the first few days following treatment to the sinuses we find the nasal symptoms are increased in intensity. During the chest series we may encounter a few cases in which a transitory nausea is disturbing, but these are easily controlled. Conversely, however, we do see the occasional case in which there is an initial striking improvement which occurs within 24 to 48 hours after the first treatment. We have not been able to explain this or to assess its importance. We generally see a gradual improvement of the entire condition of the patient within four to six weeks which persists for a variable period of time up to several months or even indefinitely. The patients have fewer colds, or they may experience a cold or an attack of other upper respiratory infection without the usual accompanying asthmatic attacks which have been an invariable accompaniment of such infections previously. The general health and feeling of well-being seems to improve, the appetite improves, and there is generally a gain of weight.

We have made it a practice to follow up these periods of treatment with x-ray restudies at about six weeks following the treatment. It is not unusual to see striking improvements in the chest and sinus findings. Occasionally, however, we see symptomatic improvements without striking improvements in the x-ray findings.

We, therefore, submit the concept of the "sino-bronchial syndrome complicating atopic asthma." We suggest x-ray treatment as a valuable aid in its management. We think it highly important to control all symptoms in these children during the period of years when their growth processes are active and during which time it is desirable to control all symptoms possible in an effort to minimize the irreversible imprint incident to long-continued asthma:

#### SUMMARY

1. Many asthmatic children are not well controlled by allergic management.
2. Some of these present the sino-bronchial syndrome.
3. The diagnosis can only be made by careful observation, laboratory, and x-ray studies and a failure of allergic management.
4. X-ray treatment offers a safe, convenient means of favorably influencing the course of this syndrome.

## COMBINED TYROTHRYCIN-PENICILLIN THERAPY IN CONTACT DERMATITIS

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RECENTLY I had two cases, in women, of severe acute contact dermatitis. The first, a woman of thirty-eight, developed her lesions as a result of frequent exposure to a commercial antiseptic solution called Germotox. The dorsa of both hands and forearms were markedly involved with pigmentation, extreme vesiculation, much weeping and intense itching. There were also discrete large vesicular lesions on both lower legs. A patch test with Germotox was violently positive. The lesions looked so very much like burns that tyrothrycin wet dressings on the hands and diluted Burow's solution on the legs were used continuously. In about twenty-four hours there was a decided improvement of the hand lesions while those on the legs remained red and weeping. A change to tyrothrycin on the legs was very satisfactory.

After about two days of tyrothrycin packs, concomitant intramuscular penicillin (200,000 units per day) therapy was started and healing was considerably accelerated. The original pathologically pigmented areas on the hands disappeared rapidly and the entire skin was completely healed in three weeks.

The second patient had a history of previous contact dermatitis and this time developed her dermatitis following the application of a "cold wave" to her hair. She had marked vesiculation and itching on her fingers and dorsa of the hands and toes. Application of continuous tyrothrycin wet packs resulted in immediate cessation of the itching. Supplementary treatment with 200,000 units of penicillin daily by the oral route caused the blebs to disappear in a few days and the entire process cleared completely in a matter of three weeks.

It is a well-known fact that this and other types of eczema-dermatitis can last for many weeks with the ordinary wet soak treatment (Burow's permanganate, boric acid). My concept of the reason for this persistence is as follows—the skin in eczema-dermatitis is essentially a devitalized or dead tissue and the semi-saprophytic bacteria in the skin (mainly, staphylococci) grow well in this medium and produce a low-grade irritative condition which prolongs the weeping indefinitely and delays healing. In tyrothrycin, we have a superb antibiotic which destroys the surface organisms and permits rapid healing. The penicillin affects the more deeply implanted organisms which the tyrothrycin cannot reach.

I am continuing this work with combined tyrothrycin-penicillin and would suggest that these relatively harmless substances be used by others for early and/or persistent cases of eczema dermatitis and skin fungus infections. I would be glad to hear of results attained by others.

†Associate Fellow, American College of Allergists.

# Editorial

*The opinions expressed by the writers of editorials in the ANNALS are individual and do not necessarily represent the group opinion of the Board or of the College.*

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## THE RECENT FALL GRADUATE INSTRUCTIONAL COURSE

The most interesting and educational course in allergy ever presented was the Fall Graduate Instructional Course given by the College at Thorne Hall, Northwestern University, Chicago, November 5-10, inclusive.

There were 186 registrants, including ninety-five who were in the Service. The course was available to Fellows of the College, as well as to candidates for Active and Associate Fellowships.

On another page in this issue, in an announcement of the comprehensive outlines of the lectures, including references, now available and punched to fit a loose-leaf notebook, are listed the instructors and their topics.

Each course was very closely attended from nine a.m. to six p.m., with one hour for lunch throughout the entire week.

Outstanding leaders from the various specialties emphasized the manifestations of allergy to be met in their practice in a manner which precludes the mentioning of any particular presentation.

On the last morning of the course, an unscheduled surprise consisted in the showing of technicolor films of bronchoscopic observations of allergic changes in the trachea and lungs by Dr. Paul Höltinger, Chicago. There were also round-table discussions which included many practical and valuable suggestions of clinical allergy, as well as practical demonstrations of laboratory procedures, the various methods of skin testing, the making and standardization of extracts, et cetera.

The College is deeply grateful to the members of the faculty who came from all parts of the United States to present the course and to all the registrants for their attendance and close attention.

F. W. W.

## HOUSE DUST

In the course of the recent Fall Graduate Instructional Course in Allergy of the College, a distinguished dermatologist paid vigorous disrespect to the time-honored inhalant allergen, house dust, which was discovered by R. A. Cooke. The speaker, charged first that our knowledge about the "dust allergen" is unscientific, secondly, that its original material is an entirely uncontrollable, highly variable mixture of unknown substances, and thirdly, that its specific content represents not a specific dust allergen but only a varying mixture of "contaminating" allergens.

The reader may decide for himself whether empiricism cannot be scientific and whether empirical findings can be dependable as well as medically useful. We can heartily agree with the speaker's second charge,

pointing out, however, that the same complaint applies in greater or less degree not only to pollen extracts but to the preparations of all the so-called protein-allergens, excepting perhaps that of ovomucoid, which represents possibly the nearest approach to a solution of a single protein.

Apropos of his third authoritative pronouncement, we would ask the speaker to explain the following:

1. Like the pollen-atopen (which is probably a polypeptide—Abramson et al., Rockwell) the dust allergen is relatively indigestible, although the contaminating protein in dust extract like the protein of common allergens is easily digestible (Grove-Coca, Rockwell).

2. The antigenic quality of the dust allergen is similar to that of the pollen allergen and different from that of native protein (M. Walzer and associates).

3. The content of the dust allergen in vacuum cleaner material from bed mattress, or much used automobile seats is ten to twenty times as great as such material obtained from the floor rugs (Efron, confirmed by the writer and E. L. Milford). How can "mixed allergic contaminants" become concentrated in those two places? We know of the dog in the manger but not of the cat and dog, et cetera, in the mattress.

4. Many dust-sensitive persons, including especially those non-reaginitically sensitive to the dust allergen, are greatly relieved of their symptoms through the covering of mattresses, pillows and upholstered furniture with dustproof covers. This empirical fact also suggests the development of the dust allergen in the stuffing of these articles (Milton Cohen), perhaps under the influence of body warmth and moisture.

The origin and nature of the house-dust allergen remain an intriguing problem. Certainly, the facts just recited, whether they be "scientific" or not, seem to oppose formidable difficulties in the way of the hypothesis of the "mixed contaminating allergens," which, by the way, was rejected by Cooke in his original report.

A. F. C.

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## THE SAN FRANCISCO SESSION

There will be a marked restriction of hotel reservations in San Francisco owing to the number of collateral societies meeting at the same time. The one hundred twin-bed rooms, reserved by the College for the first three days of its session will be first apportioned to the participants on the program, officers of the College, and members of the committees. Reservations may be made through the Administrative Office, 401 La Salle Building, Minneapolis, until the College reservations are exhausted. College headquarters will be at the Hotel Clift, Gary and Taylor Streets. Please specify the exact time reservations are desired, and mention that you are attending the meeting of The American College of Allergists.

Members wishing to present papers should communicate with Dr. Rudolf L. Baer, Chairman of the Program Committee, 962 Park Avenue, New York, N. Y.



# Questions and Answers

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It has come to my attention that there is now marketed a combination of Neo-Synephrine with sulfathiazole. It is also combined with aminophylline and phenobarbital and known as Adnephrin. I would appreciate it if you would answer the following questions and include the formulas.

M. D., Texas

## 1. Does Neo-Synephrine Sulfathiazolate contain sodium sulfathiazole?

No. A 5 per cent solution of sodium sulfathiazole is strongly alkaline (pH 10-11). Neo-Synephrine Sulfathiazolate is a soluble onium salt of Neo-Synephrine base and sulfathiazole whose solutions are only slightly more alkaline than that of body fluids. The 0.6 per cent solution has a pH of 7.8.

## 2. Since Neo-Synephrine rarely produces central nervous stimulation, what is the function of phenobarbital in Adnephrin?

Phenobarbital is a widely used depressant of the central nervous system and is included in many prescription specialties. It diminishes discomfort through mild sedation and is not present in this formula to counteract the side-effects which usually accompany other sympathomimetic compounds. Its inclusion with Neo-Synephrine Hydrochloride and aminophylline provides a combination capable of bringing about sedation, decongestion of the respiratory passages and bronchodilatation.

## 3. What is the duration of vasoconstrictor action of Neo-Synephrine Hydrochloride Solution?

Because of the variation in response of individual patients, and particularly so under varying conditions, this is difficult to answer definitely. However, Fitzhugh, Grant and the other investigators who have studied the duration of action under controlled conditions are agreed that Neo-Synephrine is more prolonged in action than ephedrine solution. The  $\frac{1}{4}$  per cent solution may be said to exhibit vasoconstriction of from  $1\frac{1}{2}$  to 3 hours as an average; the 1 per cent solution from 2 to 6 hours. It is worthy of note that although more prolonged in action than epinephrine or ephedrine, compensatory hyperemia is less likely to attend the use of Neo-Synephrine than follows epinephrine, privine, or, to a lesser degree, ephedrine.

Neo-Synephrine Hydrochloride is orally active and rarely occasions the symptoms of central nervous system characteristic of ephedrine. It is now available in capsules in combination with aminophylline and phenobarbital (Adnephrin, Frederick Stearns Company Division) for the relief of asthmatic paroxysms. They contain:

Neo-Synephrine Hydrochloride	20 mg. (0.3 gr.)
Aminophylline	194 mg. (3.0 gr.)
Phenobarbital	16 mg. (0.25 gr.)

Could you supply me with references to the lecture on the Physiologic Aspects of Allergy delivered by Dr. H. A. Abramson at the College Instructional Course held at Chicago, November 5-10, 1945?

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(Continued on Page 460)

# News Items

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Dr. B. Edgar Spiegel, 25 Central Park West, New York City, has been appointed Director of Allergy and attending allergist to Midtown Hospital, New York City.

\* \* \*

The Board of Regents is pleased to announce the election to Honorary Fellowship of Dr. Bayard T. Horton, Mayo Clinic, Rochester, Minnesota, for his investigative and clinical researches in allergy.

\* \* \*

Dr. Bennet Kraft is now out of the service and has opened offices at 760 Bankers Trust Bldg., Indianapolis, Indiana.

\* \* \*

Dr. L. E. Seyler has returned from service in the Navy and has re-established his office in the Harries Building, Dayton, Ohio.

\* \* \*

Major Alexander R. Altose (MC) is being treated at the Borden General Hospital, Chickasha, Oklahoma, for an injury. He plans to return to his private practice at Seattle, Washington, by spring.

\* \* \*

Dr. Henry L. Turkel, 1700 Grand Concourse, New York City, Chief of Allergy Division, Lenox Hill Hospital, New York, has been appointed Adjunct Professor in Medicine (Allergy) and also Chief of the Allergy Department at the New York Polyclinic Medical School and Hospital of New York City.

\* \* \*

Dr. Alfonso Grana, Chief, Nutrition Clinic, Department of Allergy (Clinic of Professor Beguino Varela Fuentes), Montevideo, Uruguay, is at the present time an Assistant at the Institute of Experimental Medicine, Guggenheim Fellowship, Mayo Clinic, where he is doing investigative work in anaphylaxis. College headquarters was recently honored by a visit from him.

\* \* \*

This is a reminder to members in the Service, who have now been discharged and whose membership dues were deferred while in the Service, that payment is now due. A reasonable time will be extended until private practice can be resumed for those who desire it.

\* \* \*

Dr. Leon Bentolila, who recently was in the United States doing graduate work in allergy, has now returned to Argentina. He has been assigned Head of the Allergy Department of the Rosario Medical School and is engaged part time in private practice at San Lorenzo 1150, Rosario, Argentina.

\* \* \*

Notice to members of the College and subscribers to the ANNALS OF ALLERGY outside the United States:

Because of the wide differences of foreign money exchange, payment for membership fees, annual dues, and subscriptions to the ANNALS OF ALLERGY should be sent either by International Post Office Money Order or by Bank Draft in United States money values.

## NEWS ITEMS

The following have made contributions to the College Research Fund since publication of the September-October issue of the ANNALS:

Dr. Carlyle B. Bohner, 822 Hume Mansur Bldg., Indianapolis, Indiana ..\$ 50  
Dr. Pearl L. Zinc, 533 Medical Arts Building, San Antonio, Texas .....\$ 50  
Dr. Gerald C. Grout, Suite 1080, Fidelity Medical Bldg., Dayton, Ohio....\$100  
Dr. Albert H. Braden, 1704 Crawford Street, Houston, Texas .....\$100

There are now sufficient research funds to pay for the first year's stipend of all three Fellowships which have been established by the College. These three Fellowships will now become active, since trained men are expected to be available with the return of available men from the Service.

\* \* \*

The American College of Allergists is happy to announce that Professor Doctor Robert Doerr of Basel, Switzerland, has graciously accepted an invitation to be guest speaker at the next Annual Meeting of the College in San Francisco in July, 1946.

Dr. Doerr, who is one of the founders of modern immunology, described the mechanism of antibody formation as early as 1909, his work subsequently being confirmed by Heidelberger. Professor Doerr showed that the anaphylactic passive sensitizing effect of sera was found to be quantitatively proportional to the precipitin contents of these sera. He proved conclusively that parts of an antigen do not enter into the composition of an antibody and later did a great deal of fundamental work dealing with Forssman antigens. Especially interesting to physicians practicing allergy are the basic studies done by Dr. Doerr in the field of passive sensitization.

Further details regarding Dr. Doerr's proposed visit to this country will be announced in future issues of the ANNALS.

\* \* \*

We are pleased to announce the return from service of the following members of the College and their present office locations: Lt. Col. Harold A. Abramson (MC), 57 West 57th Street, New York City 19; Capt. Meryl M. Fenton (MC), at his former location, 1212 Eaton Tower, Detroit 26, Michigan; Capt. John D. Gillaspie, First National Bank, Boulder, Colorado; Capt. Matthew Ginsburg (MC), 2202 Vermont Avenue, Toledo, Ohio; Lt. Col. Albert S. Hanser (MC), 3424 Longfellow Boulevard, St. Louis, Missouri; Capt. Joseph H. Hersh (MC), 57 West 57th Street, New York City 19; Capt. Harry Mullin (MC), 206 Medical Arts Building, Scranton, Pennsylvania; Lt. Col. Robert B. Radl, Quain and Ramstad Clinic, Bismarck, North Dakota; Lt. Comdr. James E. Stroh (MC), Stimson Building, Seattle, Washington; Major David R. Thomas, Jr., Southern Finance Building, Augusta, Georgia; Lt. Col. George W. Warrick (MC), 900 South 20th Street, Birmingham, Alabama.

### SOUTHWEST ALLERGY FORUM

The Southwest Allergy Forum will hold its next annual meeting at Houston, Texas, April 8 and 9, 1946. The Executive Committee consists of Dr. George W. Owen, Chairman, Jackson; Dr. Albert H. Braden, Secretary-Treasurer, Houston; Dr. Herbert Rinkel, Kansas City; Dr. Henry Ogden, New Orleans; Dr. Orval Withers, Kansas City. Dr. Chauncey Leake, Dean of the Texas Medical School, is to be the guest of honor, and will discuss "The Pharmacological Evaluation and Clinical Application of the Various Drugs Used by Allergists." The improvement of traveling facilities, as well as the time of the year, warrants a very good attendance. There is a spirit of cordiality and informality at these meetings, where the local problems of the members are freely discussed. The program will be announced in a future issue of the ANNALS.

## SECOND ANNUAL MEETING

The second annual meeting of the American College of Allergists will be held at the Clift Hotel, San Francisco, Saturday and Sunday, June 29 and 30, 1946. On Friday, June 28, for one half day, the Pan-American Congress will be held under the auspices of the College, the other half day will be devoted to a Section on Experimental and Comparative Allergy.

The College has made 100 hotel reservations for the three days of the College session. All those desiring reservations to extend throughout the American Medical Association session, which will be conducted at the Civic Auditorium, San Francisco, from July 1 to 5 should notify the Secretary as soon as possible, giving the exact time for their reservations. Hotel reservations should be made immediately as the College cannot assure securing more than 100 twin-bed rooms. When these are filled, it will be necessary for those who wish to attend, to make their own reservations.

A cocktail hour at 6:15 on Saturday evening, June 29, will precede the informal dinner that evening. Luncheons will be served at the Clift Hotel at 12:30 p.m. Saturday and Sunday, June 29 and 30.

An excellent scientific program is now being arranged covering all phases of the subject of allergy. It is proposed to have four fifty-minute papers, with ten minutes allowed for discussion, from 11 a.m. to 12 m., and from 2 to 3 p.m., on Saturday and Sunday, including the guest speaker, Professor Robert Doerr, University of Basel, Basel, Switzerland. For the remainder of the time a half hour each will be allowed for fifteen- and twenty-minute papers, with the remainder of the time for discussion. On Saturday afternoon, a symposium will be presented with questions and answers on selected subjects.

The president's address will be delivered Sunday afternoon at 3:30 p.m., followed at 4 p.m. by the business meeting. Dr. Homer Prince, Houston, Texas, is planning a scientific program by the Association of Allergists for Mycological Investigation Friday evening, June 28, at the Clift Hotel.

## INSTRUCTIONAL COURSES AVAILABLE

Printed sets of the comprehensive outlines of lectures, including references, of the Fall graduate instructional courses presented by the College at Northwestern University, Chicago, Illinois, November 5 to 10, inclusive, are available for \$6.00 a set. These are perforated to fit a standard ring book, as formerly. Please mail orders to American College of Allergists, 401 LaSalle Medical Building, Minneapolis 2, Minnesota. Several lectures were stenotyped, and copies of these will be included with the printed set when ready.

### Fundamentals of Allergy—Immunologic.

FRED W. WITTICH, M.D., Minneapolis, Minn.

### Fundamentals of Allergy—Physiologic

MAJOR HAROLD ABRAMSON (MC), Edgewood Arsenal, Md.

### Experimental Allergy

PAUL R. CANNON, M.D., University of Chicago, Chicago, Illinois

### Preparation of Pollen Extracts

GEORGE E. ROCKWELL, M.D., Milford, Ohio

### Histopathology of the Allergic Reaction

BERNARD STEINBERG, M.D., Toledo Hospital Institute of Medical Research, Toledo, Ohio

### Materia Medica of Allergy and Pharmacology of Drugs Used in Allergy

CARL DRAGSTEDT, M.D., Northwestern University Medical School, Chicago, Illinois

### Allergy of the Nose and Paranasal Sinuses—Perennial Allergic Rhinitis

FRENCH K. HANSEL, M.D., Washington University, St. Louis, Missouri

### Botany of Hay-Fever Plants

ROGER P. WODEHOUSE, Ph.D., Associate Director of Research in Allergy, Lederle Laboratories, Pearl River, New York

## NEWS ITEMS

### Ocular Allergy

A. D. RUEDEMANN, M.D., Cleveland Clinic, Cleveland, Ohio

### Serum Disease

BRET RATNER, M.D., New York University College of Medicine, New York, New York

### Allergy from Drug and Biological Products

JONATHAN FORMAN, M.D., Ohio State University Medical School, Columbus, Ohio

### Reaction from Blood Transfusion

ANDREW IVY, M.D., Northwestern University Medical School, Chicago, Illinois

### Bronchial Asthma (1st session)

LEON UNGER, M.D., Northwestern University Medical School, Chicago, Illinois

### Inhalation Therapy of Bronchial Asthma (2nd session)

ALVAN L. BARACH, M.D., Columbia University College of Physicians and Surgeons, New York, New York

### Dermatologic Allergy—Atopic Dermatitis (1st session)

LOUIS R. BRUNSTING, M.D., Mayo Clinic, Rochester, Minnesota

### Dermatologic Allergy—Urticaria (2nd session)

RUDOLF L. BAER, M.D., New York Post Graduate Medical School of Columbia University, New York, New York

### Dermatologic Allergy—Contact Dermatitis (3rd session)

LOUIS SCHWARTZ, M.D., Medical Director, Chief Dermatoses Section, U. S. Public Health Service, Bethesda, Maryland

### Pediatric Allergy—The Differential Diagnosis of Bronchial Asthma in Infants and Children (1st session)

JEROME GLASER, M.D., University of Rochester Medical School, Rochester, New York

### Pediatric Allergy—Status Asthmaticus (2nd session)

JOSEPH R. WISEMAN, M.D., Syracuse University, Syracuse, New York

### Pediatric Allergy—Respiratory Pollen Allergy in Children (3rd session)

M. MURRAY PESHKIN, M.D., New York, New York

### Pediatric Allergy—Dermatologic Allergy in Children (4th session)

JOHN H. MITCHELL, M.D., Ohio State University Medical School, Columbus, Ohio

### Allergy of the Central Nervous System—Migraine (1st session)

FOSTER KENNEDY, M.D., Cornell University Medical College, New York, New York

### Allergy of the Central Nervous System—Ménière's Disease (2nd session)

BAYARD T. HORTON, Mayo Clinic, Rochester, Minnesota

### Physical Allergy

CECIL KOHN, M.D., Kansas City, Missouri

### Allergic Bronchitis and Bronchiectasis

J. WARRICK THOMAS, M.D., Vaughan Memorial Clinic, Richmond, Virginia

### Clinical Use of Histamine

BAYARD T. HORTON, M.D., Mayo Clinic, Rochester, Minnesota

### Diagnosis of Hay Fever

HARRY L. ROGERS, M.D., Jefferson Medical College, Philadelphia, Pennsylvania

### Treatment of Hay Fever

HARRY L. ROGERS, M.D., Jefferson Medical College, Philadelphia, Pennsylvania

### Gastro-intestinal Allergy

ORVAL R. WITHERS, M.D., University of Kansas School of Medicine, Kansas City, Missouri

### Miscellaneous Allergies—Agranulocytosis

THERON RANDOLPH, M.D., Northwestern University Medical School, Chicago, Illinois

### Mold Allergy

HOMER E. PRINCE, M.D., Baylor University, Houston, Texas

### Less Common Manifestations of Allergy—Epilepsy, Loeffler's Syndrome, Joint Allergy, Purpura and Genito-urinary Allergy

J. WARRICK THOMAS, M.D.: Vaughan Memorial Clinic, Richmond, Virginia.

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## COLLEGE REGIONAL SPRING INSTRUCTIONAL COURSE IN ALLERGY

The Pacific Northwest Instructional Course in Allergy for physicians wishing to refresh their knowledge of the subject and those training for specialization in allergy will be held at the University of Oregon Medical School, Portland, Monday, Tuesday, and Wednesday, March 4, 5, and 6.

Every phase of allergy will be presented by competent authorities. The hours will be from 9 to 12:15 and from 2 to 5:15. There will be seminars, personal discussions and practical demonstrations of simple laboratory and diagnostic procedures.

For details write to Dr. Merle Moore, 607 Medical Arts Building, Portland 5, Oregon.

## Questions and Answers

(Continued from Page 455)

28. The nature of the ragweed pollen allergen. *Tr. N. Y. Acad. Sci.*, 4:55, 1941.
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## Fatigue and Weakness of Allergic Origin

(Continued from Page 430)

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# BOOK REVIEWS

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IMMUNO-CATALYSIS. By M. G. Sevag, Ph.D., with a Preface by Stuart Mudd, M.D. 272 pages. Price \$4.50. Springfield, Illinois: Charles C. Thomas, 1945.

Doctor Sevag is Assistant Professor of Biochemistry in Bacteriology, Department of Bacteriology, School of Medicine, University of Pennsylvania, Philadelphia.

In this timely monograph the author has succeeded in correlating the fields of enzyme chemistry, immuno-chemistry and the mechanisms of infectious disease. There is an arrangement of experimental data little known to most students of immunity and infectious disease which clearly shows the interdependence between the phenomena of immunity and of biocatalysis. Doctor Sevag shows that enzyme and immune reactions are often similar when determining specificity.

The first three sections of the book bring together many experimental facts of mutual interest to both specialists in enzymology and immunology.

Part I deals with antigens as biocatalysts. In it are discussed the formation and properties of antibodies, including their chemical nature, the physicochemical properties of normal and immune serum globulin and their molecular weights; electrophoretic mobilities and their isoelectric points; the role of catalysis in chemical reactions and its bearing on antibody formation; the common characteristics of inorganic catalysts, enzymes and antigens; the mechanism of antibody formation.

Part II discusses the antibody as a specific enzyme inhibitor, including the nature of the analogy between immune and enzyme reactions, the formation of specific inhibitors in enzyme reactions, such as pepsin, trypsin, certain acids and their salts.

Part III is a reservoir of information on antienzyme immunity.

Part IV presents in detail immunity against various bacterial enzymes including bacterial toxins, hemolysins, the permeability factor, bacterial carbohydrases and proteinases.

The problem of antibody formation against respiratory enzymes is fully discussed in Part V.

Every student and specialist of immunity and of infectious diseases will have a far better insight into this increasingly important subject when making practical application to their studies by using the text as a guide.—F.W.W.

ESSENTIALS OF CLINICAL ALLERGY. By Samuel J. Taub, M.D., 198 pages. Illustrated. Price \$3.00. Baltimore: The Williams and Wilkins Co., 1945.

The author Professor of Medicine, Cook County Graduate School of Medicine, particularly interested in allergy, has succeeded very well in writing a manual which is refreshingly practical but as complete and informative as a small book can be when treating such a detailed subject.

There are twenty-two chapters. The book is a reservoir of succinct data, considered with a broad insight of the subject and correlated in a compact manner. The early chapters present immunologic chemistry and its relation to clinical allergy, the anatomy of allergy, and gives details in the diagnosis and treatment of hay fever in all its forms. The latter half of the book is devoted to the etiologic diagnosis and treatment of asthma, dermatologic allergy and the miscellaneous allergies, which now embrace about fifteen diseases.

There are history forms, lists of allergens, detailed directions for administration, dosage schedules, methods of preparing extracts, instructions to patients for special diets, and recipes, making this an excellent manual of clinical diagnostic procedures.

The student of allergy, as well as the specialist, will find this a handy reference book at all times.—F.W.W.



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